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18

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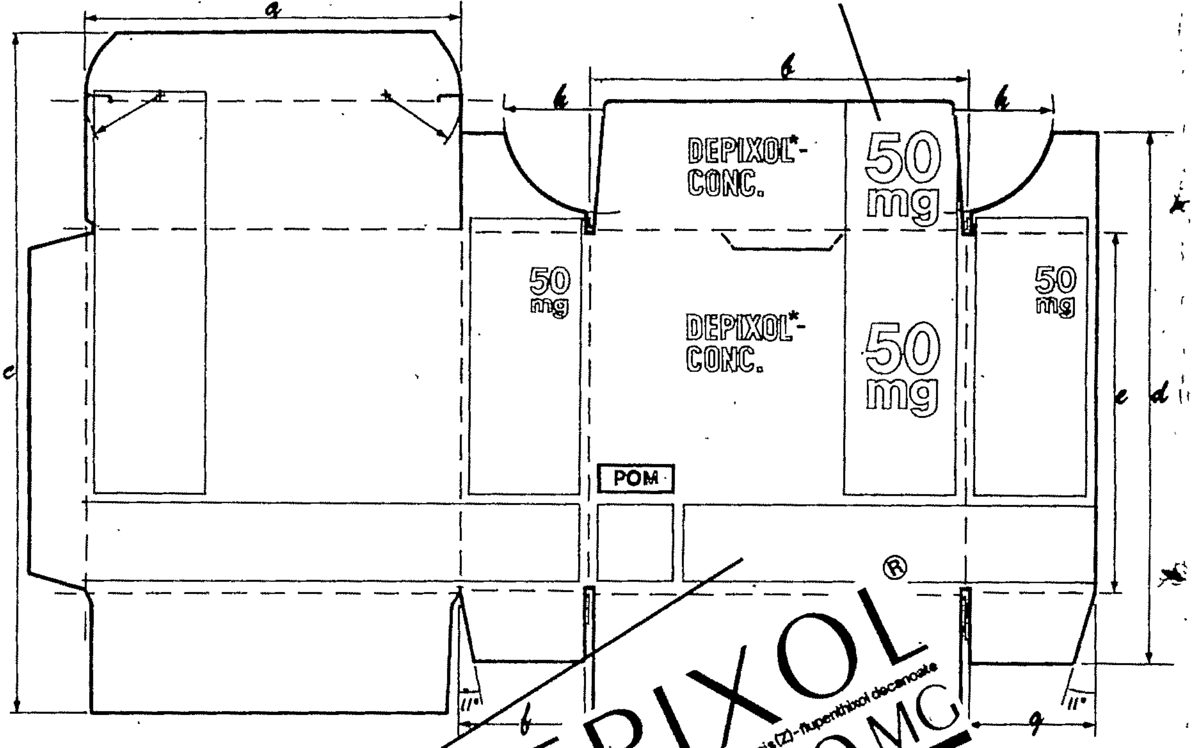

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May 1989 Volume 154

Review Articles

The impact of molecular genetics on our understanding of the psychoses. *M. J. Mullan and R. M. Murray* 591

Dementia and Parkinson's disease. *W. R. G. Gibb* 596

Comment

Community care and the difficult and offender patient. *T. D. Scannell* 615

Papers

The Glasgow rehabilitation survey. *M. G. Livingston and A. Bryson* 620

Community management of schizophrenia. A two-year follow-up of a behavioural intervention with families. *N. Tarrier, C. Barrowclough, C. Vaughn, J. S. Bamrah, K. Porceddu, S. Watts and H. Freeman* 625

Family history and cerebral ventricular enlargement in schizophrenia: a case control study. *M. J. Owen, S. W. Lewis and R. M. Murray* 629

A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms. *D. Dodwell and D. Goldberg* 635

A family study of two subgroups of schizoaffective patients. *M. Maj* 640

A comparison of in-patient and out-patient prescribing. *D. N. Anderson* 644

The relationship between depression and hopelessness. Implications for current theories of depression. *S. M. Greene* 650

The hormonal environment of post-natal depression. *B. Harris, S. Johns, H. Fung, R. Thomas, R. Walker, G. Read and D. Riad-Fahmy* 660

Depression following spinal cord injury: a prospective in-patient study. *F. K. Judd, J. Stone, J. E. Webber, D. J. Brown and G. D. Burrows* 668

A rating scale for drug-induced akathisia. *T. R. E. Barnes* 672

Quality of parenting in alcoholics and narcotic addicts. *E. Bernardi, M. Jones and C. Tennant* 677

Anorexia nervosa in Hong Kong. Why not more in Chinese? *S. Lee, H. F. K. Chiu and C. Chen* 683

'Asneezia' – some further observations. *G. D. Shukla* 689

Case Conference

Thirty years' war: a battle with insomnia. *J. R. Newton, C. Shapiro and A. Stewart* 691

Point of View

The damnation of benzodiazepines. *F. Kräupl Taylor* 697

Brief Reports

The occurrence of depression following mania: a method of predicting vulnerable cases. *C. P. Lucas, J. C. Rigby and S. B. Lucas* 705

Alexithymia, masked depression and loss in a holocaust survivor. *R. Z. Fisch* 708

Two cases of agranulocytosis on addition of a butyrophenone to a long-standing course of phenothiazine treatment. *A. H. Young and R. Kehoe* 710

Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana. *R. Tandon, D. Dutchak and J. F. Greden* 712

De Clérambault's syndrome (erotomania) in organic delusional syndrome. *Y. Y. El Gaddel* 714

Delusions of pregnancy in men. Case report and review of the literature. *S. K. Chaturvedi* 716

Correspondence 719

A hundred years ago. Researched by Henry Rollin 733

Books Reconsidered

A critical dictionary of psychoanalysis. *C. Rycroft* 734

Book Reviews 738

American Journal of Psychiatry, Volume 146, Number 4, April 1989 750

The Journal of Nervous and Mental Disease, Volume 177, Number 4, April 1989 *facing* 750

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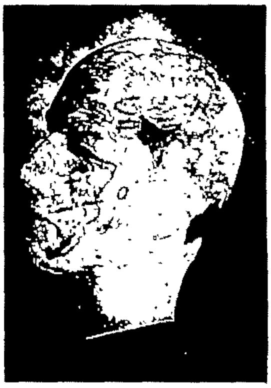

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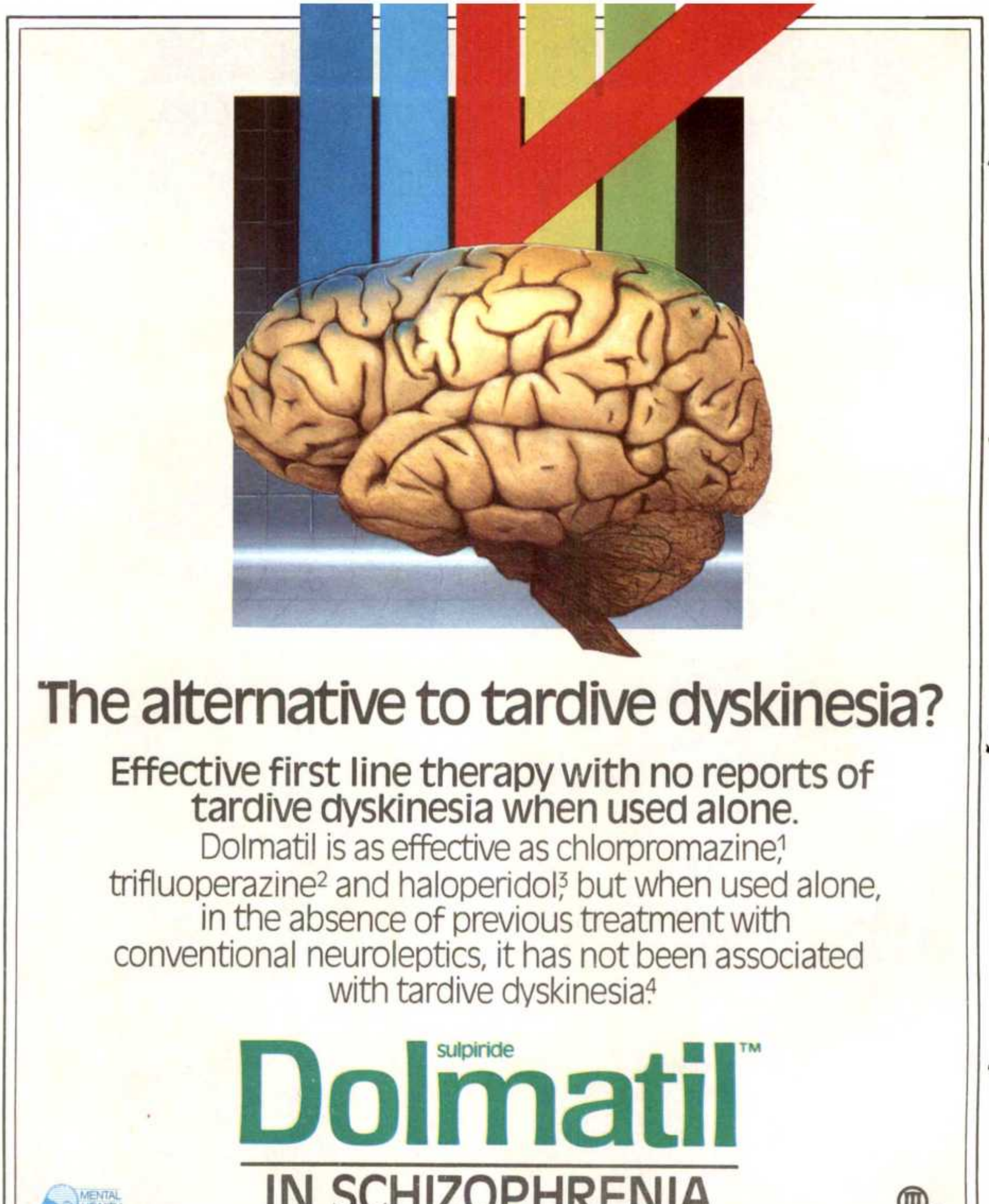

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Review Article

The Impact of Molecular Genetics on Our Understanding of the Psychoses

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Studies demonstrating the linkage to separate chromosomal locations of Alzheimer's disease, manic depression, and schizophrenia require re-evaluation of our ideas of their genetic aetiology. This article reviews the findings, and explores the increasing contribution of the 'new genetics' to our understanding of the organic and functional psychoses.

Over the last decade, articles describing the identification of linkage markers, and indeed the genes responsible, for diseases have filled the journals, and fields as diverse as haematology and cancer research have been quite transformed (Weatherall, 1985). Recombinant DNA technologies have only recently begun to be applied to psychiatric disorders, and therefore their potential impact is only now being realised (Baron & Rainer, 1988; Whatley *et al*, 1988). However, the fact that the linkage approach with DNA markers enables researchers to track down genes for disorders of largely unknown aetiology and pathogenesis makes this strategy particularly well suited to the study of the major psychoses.

Medical models

DNA markers, or more specifically, restriction fragment length polymorphisms (RFLPs) are generated by cutting DNA with enzymes (endonucleases). The recognition sites for these enzymes vary harmlessly between individuals, reflecting differences in the base-pair sequence of the DNA. As a result, cutting the DNA of different individuals produces characteristically different lengths of DNA. Such variations are inherited in a simple Mendelian fashion. They can therefore be used as identification tags, so that if a disease can be linked to a marker RFLP, then a susceptibility gene for the disease must lie nearby on the same chromosome. In this way researchers have traced mutant genes through families, and determined, for example, that the genes for cystic fibrosis and Huntington's disease lie on chromosomes 7 and 4 respectively. Once the approximate chromosomal location is known, then a variety of other techniques (see Baron & Rainer, 1988) can be used to identify the precise site and sequence of the gene, and indeed characterise the protein it produces. Reviews of these techniques are available elsewhere (Weatherall, 1985; Gurling, 1985; Davies, 1986).

Huntington's disease has served as a prototype for research into single-gene disorders. Gusella *et al* (1983) demonstrated linkage to a marker on chromosome 4. Now the location of the defective gene is known with sufficient precision to allow reliable pre-symptomatic diagnosis of individuals 'at risk' (Wasmuth *et al*, 1988). It is only a matter of time before the defective gene is isolated, sequenced, and its product identified; at this point, where linkage studies are superseded by sequencing, research into aetiology becomes research into pathogenesis. It is, of course, true that several features of Huntington's disease expedited its tight linkage. The disease was known to be a discrete homogeneous entity, and both the mode of transmission (autosomal dominant) and penetrance (100%) were established. Thus, the confounding problem of genetic heterogeneity in different families was absent, and two of the parameters that must be estimated in most computer linkage programs could be accurately determined.

The mode of transmission of the common organic and functional psychoses is obviously quite different from that of Huntington's disease and other single-gene disorders. However, it is not so different from that in other common disorders with a genetic component, such as the familial cancers, coronary heart disease, or diabetes, which do not show simple Mendelian patterns of inheritance (Bock & Collins, 1987; Scott, 1987). The aetiology of such disorders has been regarded as multifactorial. Thus, Gottesman & Shields (1972) conceptualised schizophrenia as a multifactorial polygenic disorder, and this was widely accepted as a means of correctly expressing the risk to relatives and of estimating approximate heritability. The disadvantage of such models is that, while they are hard to fault statistically, they do not provide any biological insight into the nature or number of genes involved in a disease or their mechanism of action. It is now clear that the new DNA technologies provide the means to dissect the statistical concept of multifactorial disorder into its constituent genetic and non-genetic components. Indeed, Weatherall (1987) believes that it is in the investigation of the common multifactorial disorders that molecular genetics will play its most important role.

Coronary heart disease, the multifactorial disease in which most progress has been made, provides a model of how genetic variance in liability to such a disorder can be broken into its constituent parts. One of the first components to be characterised was familial hypercholesterolaemia – individuals heterozygous for the causal gene have twice the normal level of circulating low-density lipoprotein, and in consequence are prone to heart attacks early in adult life (Davis, 1987). Although this gene devastates the affected families, it accounts for only a small proportion of heart attacks in the population. In general, more subtle genetic variations are the rule, and researchers are now well on their way to assessing the relative importance of genes coding for (a) apolipoproteins, (b) lipoprotein receptors, (c) the enzymes which regulate cholesterol synthesis, and (d) high levels of fibrinogen. Thus the 'polygenes' of this multifactorial disorder are gradually being identified (Bock & Collins, 1987).

Familial Alzheimer's disease and chromosome 21

Alzheimer's disease was the first major psychiatric disease to attract the attention of molecular geneticists. This interest was aroused by the observation that individuals with Down's syndrome who survive into early middle age develop a dementia whose neuropathology is identical to that of Alzheimer's disease (Oliver & Holland, 1986). The fact that chromosome 21 is triplicated in Down's syndrome provided a strong clue that a putative mutant gene for Alzheimer's disease might be sited here. In some families, Alzheimer's disease segregates as an autosomal dominant disorder, and, in four such families, St George-Hyslop *et al* (1987) showed linkage with DNA markers on the proximal part of the long arm of chromosome 21. This was demonstrated by a lod score of 4.25 – a score of 3 or above is conventionally taken as proof of linkage. Further excitement followed the demonstration that the gene for the beta amyloid found in the plaques of Alzheimer's disease was in this region, and this was proposed as a 'candidate' (or causal) gene. However, it was soon shown that Alzheimer's disease did not segregate exclusively with one allele of the amyloid gene, thus disproving this suggestion (Van Broeckhoven *et al*, 1987).

Several fascinating issues have arisen from the chromosome-21 linkage. Firstly, it is not clear how much of Alzheimer's disease it accounts for; overtly familial cases are no longer thought a minority (Mons *et al*, 1987), and the gene might have such low penetrance that it could explain some apparently sporadic cases. Secondly, it appears that not all familial cases are linked to the chromosome-21 site; there may therefore be genetic heterogeneity (Schellenberg *et al*, 1988). Thirdly, the relationship between genotype and phenotype is not known, but the possibility now exists of exploring clinicogenetic correlates, and of subdividing the condition on the basis of genetic aetiology. In families in whom linkage has been demonstrated, Alzheimer's appears to show early onset and an aggressive course, but this might simply reflect the fact that it is difficult to prove linkage in families where the onset tends to be late. Fourthly, it should be possible to determine the aetiological relationship of Alzheimer's disease to other familial dementias, such as Pick's disease and dementia of frontal type (Neary *et al*, 1988).

Thus, research into Alzheimer's disease is poised for exciting advances, which will have profound clinical implications, and there is an expectation that geneticists will soon reach a similar position with manic depression and schizophrenia.

Genetic heterogeneity in manic depression

Although it is unusual for manic depression to segregate in families as though it results from a single gene, such families do exist, and the absence of father–son transmission in a number of such families led to the idea that a dominant X-linked gene might be involved (Reich *et al*, 1969). Some researchers claimed linkage with X-chromosome markers (Mendlewicz *et al*, 1980), but others were sceptical. Recently, Baron *et al* (1987) carried out a more definitive pedigree study among five Israeli families containing 161 individuals, of whom 47 had bipolar or other affective illness. Linkage was proven with the markers colour blindness and G6PD deficiency. Mendelwicz *et al* (1987) used a probe for the factor IX gene, which is known to be located on the distal long-arm of the X chromosome, in a study of ten informative families. Once again, linkage was demonstrated, with a lod score of 3.10.

Totally different, but nonetheless positive, evidence of linkage of bipolar disorder with two markers on the tip of the short arm of chromosome 11 came from a study of the Old Order Amish, a religious community in Pennsylvania (Egeland *et al*, 1987). Since the gene for tyrosine hydroxylase, one of the principal enzymes involved in the synthesis of catecholamines, is located near the markers, this has been proposed as the causal or 'candidate' gene, although as yet there is no proof that this is so. Three studies of Icelandic, American and Irish pedigrees (Hodgkinson *et al*, 1987; Detera-Wadleigh *et al*, 1987; Gill *et al*, 1988, respectively) failed to find linkage with the chromosome-11 markers. Since their pedigrees were incompatible with X-linked transmission also, the causal gene(s) in these families must lie elsewhere.

Thus, at least three genetic subtypes of bipolar illness exist, linked to genes on the X chromosome, on chromosome 11, and at another, undetermined site. No family outside the Amish has yet shown the chromosome-11 linkage, and it is possible that this mutation is confined to this genetically isolated group. X linkage is likely to be commoner, and indeed Baron *et al* (1987) claim that up to 25% of bipolar disorder may be X linked. Nevertheless, the most important task for geneticists is now to locate the gene or genes responsible for the subtype of manic depression not linked to the X chromosome or chromosome 11, which is likely to constitute the majority of cases.

The fact that at least three genes can cause manic depression is much less surprising to geneticists than it is to psychiatrists. While some of the latter have tended to consider that all cases of manic depression, or, even more curiously, that all cases of functional psychosis will have the same underlying cause, the former have become accustomed to apparently discrete clinical disorders breaking down into a variety of molecular pathologies. One such example is retinitis pigmentosa, which is now known to exist in X-linked and autosomal dominant and recessive forms. It may well be that vulnerability to manic depression will turn out to be the result of a biochemical abnormality in some final common pathway, and that a variety of genetically induced enzyme defects can produce this.

Paradoxically, an opposite tendency seems to occur – a range of diagnostic categories are found in the pedigrees that have generated the positive linkage results. The rationale for including such phenotypes as unipolar illness and schizoaffective disorder in these analyses is that these conditions occur frequently in the relatives of probands with bipolar illness (Gershon *et al*, 1982). What is striking, however, is that broadening the diagnostic categories to include such individuals as affected cases raises the lod score, i.e. the measure of linkage to the specific gene under consideration. One would have expected the lod score to fall or at most to remain constant if these cases were not genetically linked to the mutant gene, as such individuals would be scored as recombinants. However, in the Amish study, the best evidence for linkage was obtained when those considered as cases included not only bipolar individuals but also those with unipolar major depression and schizoaffective disorder; similarly, the study of Mendlewicz *et al* (1987) shows linkage to bipolar, unipolar, and cyclothymic phenotypes.

Localisation of a gene for familial schizophrenia

Most experts (e.g. Sturt & McGuffin, 1985; Kendler, 1987) had considered that it would be difficult, if not impossible, to establish linkage in schizophrenia, not only because of the inevitable diagnostic problems and possible heterogeneity, but also because of the decreased reproduction by ill individuals and the rarity of large multiply affected families.

However, the situation was changed radically by an astute observation by clinicians in Vancouver (Bassett *et al*, 1988), who ascertained not only the occurrence of schizophrenia in a Chinese proband and his maternal uncle, but also that these two had different facial features to all other members of the family. Further investigation revealed that they shared several minor physical anomalies, as well as a partial trisomy of chromosome 5, i.e. an extra segment from chromosome 5 was inserted into the long arm of chromosome 1. The proband's mother had a balanced translocation, in that she had the same extra segment in chromosome 1 but had lost equivalent material from chromosome 5; thus she had no triplicated genes, and no psychosis. Bassett *et al* (1988) suggested that if extra chromosomal material from the translocation site on chromosome 5 could cause schizophrenia, then this was 'a candidate region'.

Studies from large American laboratories (e.g. Kennedy *et al*, 1988) failed to find any linkage between schizophrenia and DNA markers in the crucial segment, and it began to look as if Bassett's hypothesis was mistaken. However, DeLisi *et al* (1988), who used the glucocorticoid receptor gene as a marker, reported preliminary results that did suggest possible linkage. Subsequently, Sherrington *et al* (1988) reported striking positive results; linkage was demonstrated with a high degree of statistical certainty between schizophrenia and two chromosome 5 probes in two English and five Icelandic pedigrees. In these families schizophrenia appeared to be inherited as an autosomal dominant condition with high penetrance, and out of 104 family members at risk, 39 had developed schizophrenia.

The researchers evaluated several models of transmission on their data, and those assuming dominant inheritance with high (86%) penetrance gave the highest lod score. Such a mode of transmission cannot account for all schizophrenia (O'Rourke *et al*, 1982), and even the protagonists of dominant transmission have assumed much lower penetrance; Karlsson (1988), for example, assumed 25%. It would not be surprising if the pedigrees in this study turned out to be atypical, for they were chosen because they did appear to show Mendelian transmission. There are two obvious possibilities. This could be an unusual dominant disorder, and its relationship to schizophrenia as a whole akin to that of familial hypercholesterolaemia to coronary artery disease. Alternatively, these families might be atypical only in showing high penetrance of the gene, and dominant transmission with low penetrance could be the general rule.

Assuming that other studies also show this linkage, we can draw a number of conclusions about the aetiology of schizophrenia. Firstly, the arguments of those who dispute a genetic contribution can be finally dismissed. Secondly, it appears that classic schizophrenia is only one of a spectrum of disorders that can arise from a mutant gene on chromosome 5. This is shown by the fact that expanding the diagnostic categories to include schizophrenia spectrum disorders, and indeed minor depression and alcoholism, as affected cases increased the lod score to 6.49. What is coded for in the mutant allele cannot, therefore, be schizophrenia *per se*, but the predisposition to develop schizophrenic psychosis and related non-psychotic illness and personality disorder. This is, of course, a similar pattern to that which emerged from the families of probands with manic-depressive illness.

Conclusions

Traditionally, nosologists have had to rely primarily on phenotypic characteristics (e.g. phenomenology and course of illness) to classify psychiatric disorder; indeed, systems such as DSM-III (American Psychiatric Association, 1980) make a virtue out of eschewing aetiological considerations. It is now clear that the same phenotype, even when based on strict operational criteria, can be the result of several distinct chromosomal lesions, i.e. several genotypes have the same phenotype. Conversely, one genotype can be associated with the development of a diverse array of psychiatric conditions. The study of Sherrington *et al* (1988) suggests that, in some families at least, schizophrenia is aetiologically related to unipolar depression, alcoholism, and personality disorder. The implications for our understanding of the pathogenesis of such conditions are that we have to explain how there is divergence from a single genotype to several phenotypes, and convergence from several genotypes to a single phenotype.

The fact that already three different genetic causes of manic depression and one of schizophrenia, to say nothing of environmental causes, are known to exist, means that nostalgic notions of unitary psychosis (Crow, 1986) can be laid to rest. Indeed, although a divergence of genotypic expression exists, classic schizophrenia and manic depression have not been shown to coexist as a result of a common genetic defect. This may be an ascertainment artefact, since families have tended to be chosen for the preponderance of a particular psychosis. An interesting exercise, therefore, would be to run chromosome 5, X and 11 probes through families containing a mixture of schizophrenic and manic-depressive relatives, and where no assortative mating had occurred.

The 'new genetics' tell us that defects at single major loci tend to predispose an individual to the development of only one of the major psychoses, with the exception of schizoaffective disorder, whose status remains unclear. The pattern emerging is one of discrete genetic lesions predisposing a core of family members with the defect to the same psychotic illness; other members of the family with the defective gene can develop related minor disorders, such as unipolar depression and personality disorder, but what they do not tend to develop, in the families studied so far, are psychotic illnesses far removed from the core diagnosis. It seems that we are about to move into a period when genetics will define disease entities in psychiatry; while genetics does not agree with any of the operationalised diagnostic systems worked out so industriously over the past 20 years, neither does it agree with alternative proposals, such as the *einheitpsychose*.

It is not surprising that aetiological heterogeneity is revealed when molecular genetic techniques are applied to diagnostic end points such as manic depression. So far, the main approach used in psychiatry has been gene mapping, with identification of the responsible gene(s) as the most important goal. It is likely that, once the gene is identified, sequenced and its protein characterised, even for a very uncommon variant, this will tell us a very great deal about the pathogenesis of the more common varieties, for it seems likely that more common causes will act through similar pathogenetic mechanisms. Certainly this has been the pattern in coronary heart disease, with familial hypercholesterolaemia, rare though it is, providing important insights into mechanisms of degenerative vascular disease.

Even before the genes themselves are identified, it is likely that allelic markers will be found sufficiently close for their reliable use in predicting genetic risk of individuals, or in differential diagnosis. Not only will we be able to do population studies with greater confidence, but the demand for genetic counselling will inevitably grow.

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Review Article

Dementia and Parkinson's Disease

W. R. G. GIBB

Recent research into the dementia of Parkinson's disease has exposed a complex area in which it has not always been possible to match clinical and pathological observations. Certain neuropsychological deficits result from a disruption of basal ganglia and frontal lobe interactions. These are unrelated to a global dementia, the prevalence of which exceeds twice that in the normal population. The associated pathological lesions comprise cortical pathology, either Alzheimer's disease or Lewy bodies, in combination with moderate degeneration of the subcortical, cholinergic, basal nucleus of Meynert.

James Parkinson's observations of six patients with the 'Shaking Palsy', published in 1817, led him to believe in "the absence of any injury to the senses and to the intellect" (Gardner-Thorpe, 1987). Consequently he suggested "that the morbid state does not extend to the encephalon", and supposed that the medulla was the site of pathology. By the second half of the 19th century, neuropsychiatric manifestations of Parkinson's disease (PD) were described (Ball, 1882), and in 1923 Lewy's monograph on PD recorded various mental derangements and dementia in as many as three-quarters of patients (Lewy, 1923). By the 1960s, dementia had become quite widely accepted as a frequent complication of later stages of the disorder (Mjönes, 1949; Loranger *et al*, 1972).

The prevalence of dementia in PD is now believed to be greater than in the general population (Mayeux, 1982), but there is still a considerable diversity of opinion on the approximate frequency of cognitive change (Taylor *et al*, 1986*a*). Widely differing estimations of prevalence are quoted, some ranging as high as 90% (Hoehn & Yahr, 1967). The last decade has seen research in this field expanding, as has other research in PD, but this flourishing interest has also been ascribed to the realisation that L-dopa fails to correct progressive cognitive impairment, despite alleviating motor disability. The discovery of the morphological and biochemical alterations associated with Alzheimer's disease (AD), particularly the depletion of cortical choline acetyl transferase (ChAT), has also encouraged the search for similar abnormalities in PD. Progress in clinical, histopathological, and biochemical areas has amassed considerable data. While uncertainties persist in a number of areas, some definite conclusions can be made. Lately there has been support for James Parkinson's view that the intellect remains intact.

The purpose of this review is to answer two questions. Firstly, how frequently does dementia occur in PD, and does it occur more often than in the general population? Secondly, is the dementia caused by AD, and if not, what is the mechanism for it? Answers to these questions necessitate an attempt to define dementia in PD, an interpretation of various cognitive changes reported in PD, and a thorough review of pathological processes. The management of dementia will not be addressed.

The diagnosis of dementia in Parkinson's disease

Interviewing patients with PD is often frustrating because of their difficulties with verbal communication, due to slowness, apparent diffidence, and disordered speech production. A slight hesitation, difficulty in finding words, and perseveration are common, so that cognitive difficulties can be suggested when these do not exist. Non-verbal communication also contributes to first impressions and in PD suggests disturbances of mood, personality, and intellect (Pentland *et al*, 1987). Silent video-recordings of four medicated patients with PD (two were stage 2 and two were stage 3 on the Hoehn and Yahr scale) and four with ischaemic heart disease were assessed using visual analogue scales concerned with aspects of personality. None of the patients showed disturbance of affect, personality, or intelligence by standard psychological tests, but remedial therapists rated the patients with PD as appearing more anxious, tense, hostile, unhappy, introverted, sensitive, passive, and less intelligent. In addition, patients may fail to appreciate the patterns of intonation and facial expression of others (Scott *et al*, 1984). Another study found that smiling in response to cartoons was reduced in patients with PD, and that this reduction correlated with higher depression scores (Katsikitis & Pilowsky, 1988). Patients with PD tend to have normal verbal content and memory, and their indifferent facial expressions seem to mask characteristically precise and analytical minds, and sometimes a dry sense of humour. Formal assessment of intellectual function is necessary before making ill informed and false assumptions about cognitive state.

There are two principal endeavours in the diagnosis of dementia in PD for the purpose of clinical and pathological studies. First is the identification of sufficient cognitive decline. The diagnosis of dementia is made difficult by the nature of its usually slow and indefinite onset. Second is the use of a robust definition sufficient for the comparison of PD and control populations. Parkinsonian motor deficits tend to impinge on diagnostic criteria for dementia by limiting activities or increasing dependency. Diagnostic criteria, as laid out in DSM-III-R (American Psychiatric Association, 1987), state that there is impairment of "short- and long-term memory, associated with impairment in abstract thinking, impaired judgement, other disturbances of higher cortical function, or personality change":

- (a) Evidence of short- and long-term memory impairment
- (b) At least one of the following
  - (i) impaired abstract thinking
  - (ii) impaired judgement
  - (iii) aphasia, apraxia, agnosia, and 'constructional difficulty'
  - (iv) personality change
- (c) (a) and (b) must interfere with work, social activity or personal relationships
- (d) these deficits must occur without delirium
- (e) either: (i) evidence of a specific organic factor related aetiologically or (ii) absence of non-organic mental disorder, such as depression.

Grades: mild - capacity for independent living exists, despite (c)
moderate - supervision is necessary
severe - continual supervision and personal care are required.

The important distinction made from 'benign senile forgetfulness' is an impairment of social or occupational functioning. Limitation of activity and increased dependency are thus features of dementia, as well as of PD.

One unavoidable drawback in any definition of dementia is that the criteria are partly subjective, so that the number of persons included in a category of mild disease is likely to vary between observers and on successive assessments. In addition, the DSM-III criteria (American Psychiatric Association, 1980) include both reversible and irreversible states. In the case of a degenerative disease, it is mostly progressive dementia that is of interest, so it is necessary to clarify whether deficits can be partly or completely reversed. For example, adjusting medication may alleviate confusion. Other drug side-effects, age, fatigue, depression, and complicating illnesses influence cognitive state (Brown & Marsden, 1987). The precise threshold for dementia remains difficult to define, but the DSM-III criteria have encouraged accuracy and provide the most reliable guide available. Accuracy might be improved by addressing only those with moderate and severe DSM-III-R dementia.

Cognitive deficits in Parkinson's disease

Quantitative assessments of cognitive state help in the evaluation of dementia and provide information such as would contribute to criteria (a) and (b) of the DSM-III-R diagnosis. In PD these quantitative assessments are confounded by two main difficulties. Firstly, some neuropsychological tests do not distinguish between motor and mental impairments, thereby allowing poor motor performance to intrude in the results. For example, in PD the performance part of the Weschler Adult Intelligence Scale (WAIS) frequently results in a lower score (mean 95.3) than the verbal part (mean 115.6; Loranger *et al*, 1972), a discrepancy which is likely to reflect motor impairment. Consequently a decline in performance IQ might not reflect dementia. Secondly, multiple mild cognitive deficits of uncertain nature, some of which may not be purely artefacts of motor tasks, have been identified in areas of memory, language, problem-solving, perceptual motor, and visuospatial skills (Reitan & Boll, 1971; Portin & Rinne, 1980; Pirozzolo *et al*, 1982).

In general, the abnormalities detected seem to be independent of a more pervasive cognitive decline, but as in the case of visuospatial disorder, they might reflect abnormality of higher cortical (parietal) function, or result from some other motor and cognitive disorder. This subject is complicated by the complexity and variation of many of the tasks that have been employed (Brown & Marsden, 1987), some of which are impaired, and some of which are not. An adequate classification of functions tested in visuospatial tasks does not exist, although Boller *et al* (1984) proposed three general categories of spatial function, namely the appreciation of the relative position of stimulus objects in space; the integration of these objects into a coherent spatial framework; and mental operations involving spatial concepts. Factors that might influence the outcome on these tasks in PD include their motor requirements, the switching of mental perspectives in spatial tasks, and the theoretical possibility of verbal rather than spatial strategies for solving tasks (Brown & Marsden, 1986).

In the case of visuospatial or perceptual motor function, some performance of constructional tasks, orientation, tracing or tracking of lines, and sequencing simultaneous movements are impaired (Schwab *et al*, 1954; Proctor *et al*, 1964; Flowers, 1978*a*,*b*; Stern *et al*, 1983). Similar deficits could be reflected in lower scores on the performance subtests of the WAIS, such as the Digit Symbol, Block Design, and Object Assembly components, compared with verbal subtests, although motor impediments may not be directly responsible. Stern *et al* (1983) studied 16 medicated patients with PD and nine controls, none of whom had dementia. Their performance on two tracing tasks was assessed by measuring both tracing velocity and accuracy. One test required the tracing of a straight line between two points and the other involved tracing a sawtooth line. Tracing accuracy was assessed by measuring the area encompassed by the deviation from the correct course. As expected, tracing velocity was impaired in the patients with PD, and was related to motor symptom severity. In addition, tracing accuracy was impaired, and performance was even less good on the sawtooth pattern, suggesting an additional perceptual disorder unrelated to that attributable to motor impairment. Flowers (1978*b*), who had found a similar tracking deficit, postulated that the inaccuracy of movement was due to a lack of predictive ability in some higher-order system. Indeed, similar deficits in tracking have been reported in animals with caudate lesions (Bowen, 1969).

Boller *et al* (1984) employed a battery of spatial tests requiring visual and motor input, but varying in the complexity of the motor response. He included tests of dementia, an information score and the Hamilton Rating Scale for Depression. He concluded that even the visuoperceptual tests requiring rather less motor response were impaired, although there was no simple relationship between the severity of PD and the visuoperceptual dysfunction. Nevertheless, some tests predominantly involved with spatial testing were normal. Della Salla *et al* (1986) used a task similar to that of Stern *et al* (1983), but as a point of difference excluded a motor component. Mildly disabled patients showed no difference compared with controls on the spatial ability requiring prediction of the point of geometrical intersection by one straight but incomplete line, and one rebounding but incomplete line. Psychometric assessment of general cognitive competence showed similar results in the two groups. Such a task does not therefore reveal an underlying visuospatial disorder, but taken with the previous study suggests that organisation of information in a strategy for movement, or the employment of movement strategies, may be defective.

In recent studies of visuospatial function, Brown & Marsden (1986) employed tests discriminating between left and right, and the mental manipulations of these right–left concepts. Independent assessments of intellectual and motor function were made. The patients did not show loss of accuracy compared with controls, or for that matter prolongation of choice reaction times, or difficulty with reversal of mental concepts (see later). Taylor *et al* (1986*a*, 1987), using a series of five visuospatial tests including object discrimination and naming, mental rotation, and right–left orientation, showed normal accuracy, but the speed of block counting was reduced. This task might be unrelated to visuospatial function, and indeed the authors pointed out that the slowness of their patients, in the presence of preserved attention, suggests bradyphrenia.

These studies of visuospatial and perceptual motor function do not therefore point to a generalised visuospatial disorder, and do not suggest a disturbance of parietal lobe function.

Among the other cognitive deficits suggested above is a defect of memory, which may be related to cholinergic deficiency (see later), but other mechanisms have recently been discussed (Sagar *et al*, 1988). Language disorder in PD generally concerns motor speech production (dysprosody, dysarthria), rather than the language deficits of AD (Cummings *et al*, 1988). Problem-solving deficits may relate to frontal lobe dysfunction in PD (see later).

Prevalence of dementia in Parkinson's disease

Comparing studies concerned with the prevalence of dementia is often impossible because of imprecise and inconsistent diagnostic criteria. Study designs and methods of assessment vary widely. In general, difficulties lie in the quantitative evaluation of dementia (as above) and the qualitative evaluation of the Parkinsonian disorder: is the disorder actually PD?

Most hospital-based surveys suggest prevalence rates for dementia of 30–40% (Brown & Marsden, 1984), but diagnostic criteria have not always been as strict as those of DSM–III (Lees, 1985). Such figures have also been challenged because of the inclusion of patients with reversible confusional states and other bradykinetic-rigid syndromes related to PD (Brown & Marsden, 1984). Reversible dementias or confusional states are frequently drug-related, but may be due to chest infections or subdural haematoma (Harding, 1984). Any one of the anti-Parkinsonian drugs may aggravate mental problems, although anticholinergics are particularly prone to do so. An example of these diagnostic difficulties is the large study of Lieberman *et al* (1979), in which 32% (168) of the patients were considered to have moderate or marked dementia, whereas only 3.4% of similarly aged spouses did. However, the criteria for those with moderate dementia were not as stringent as in DSM-III, and anticholinergics and amantadine may have been responsible for poor performances on tests of memory and intellectual function.

Pathological data suggest that there is considerable error in the average diagnosis of PD, with other Parkinsonian disorders creating confusion. For example, Forno & Alvord (1971) found that only 29 (43%) of 67 patients with undiagnosed Parkinsonian disorders showed Lewy bodies in the substantia nigra, which are the pathological hallmark of PD. In clinical studies attempting to exclude alternative, mostly non-Lewy-body Parkinsonian disorders (Gibb & Lees, 1989), diagnostic accuracy varies from 70% (Forno, 1966) to 95% (Jellinger & Riederer, 1984). Clinical diagnosis is even more uncertain in the presence of dementia, especially when this occurs early in the course of the illness. This interferes with an assessement of the effect of L-dopa, and restricts the value of observing disease progression over time. In addition to Steele–Richardson–Olszewski syndrome, other Parkinsonian disorders associated with mild to severe dementia include Alzheimer's disease with a shuffling gait or essential tremor, corticobasal degeneration, and gait apraxias due to bilateral subcortical vascular disease, communicating hydrocephalus, or trauma. Rare causes are Hallevorden–Spatz disease, Wilson's disease, repeated head trauma, and frontal lobe tumours.

Adjusting the 30–40% prevalence rate for these potential inaccuracies in the diagnosis of PD and dementia has suggested a figure of about 20% as a better estimate of irreversible, unequivocal dementia (Brown & Marsden, 1984). However, there are still doubts (Lees, 1985) that a 20% prevalence rate for dementia in PD compares with one of 5–7% for moderately and severely demented patients with AD over 65 years of age in the general population (Henderson & Kay, 1984). Lees (1985) used DSM-III criteria to diagnose dementia from the mental state examinations on 48 elderly PD patients, of mean age 74 years, and mean disease duration of 18 years. Most of the patients were severely disabled, but only seven (15%) were demented. Taylor *et al* (1986*a*) found that eight patients of unstated age among 100 (8%) referrals to the Toronto Western Movement Disorder Clinic with mild and moderate PD had clear evidence of dementia, and an additional seven had cognitive changes while on medication, four of whom improved when medication was changed. Another study quoted a figure of 7% among 36 patients, but an additional 31 patients in the original cohort either died or were lost to follow-up (Oyebode *et al*, 1986). One argument that might explain recent discrepancies is that neurologists tend to see younger patients in whom dementia is rare, whereas general physicians see an older population which is subject to an age-related rise in the prevalence of dementia; although this point is not reflected by the study of Lees (1985). It might also be argued that some figures are not generally applicable to the PD population as a whole, because general physicians and neurologists receive referrals biased towards dementing Parkinsonian patients with management problems, although these studies mostly refer to cases of dementia emerging during follow-up.

The question of age, dementia, and PD has recently been examined in young patients, because most existing surveys have been concerned with the prevalence of dementia in the over-50 age group. All patients developing PD at a young age are likely to be referred to a neurologist, and are likely to survive for a sufficient length of time to determine whether dementia is a common or invariable complication of long survival.

Quinn *et al* (1987) collected 56 patients with disease onset between age 21 and 39 years, with a median age of 35 years. None of these patients developed dementia, despite a median disease duration of 15 years, and a range of 1–35 years. The authors pointed out that only four had reached the age of 65 years. Dementia was also absent in a group of 21 patients whose disease started before the age of 39, and whose mean disease duration was 19 years (Lima *et al*, 1987). Lastly, in a study of 46 patients with disease onset before 46 years, a median age of onset of 38 years, and median disease duration of 12 years, only one patient had dementia of moderate severity (Gibb & Lees, 1988). Five patients were over 65 years. These three studies contain 123 patients with disease onset before 46 years and only one (0.8%) patient had dementia.

Another study of this kind included 49 patients with PD whose disease began before the age of 60, only one of whom (2%) was demented according to DSM-III criteria, whereas 13 of 59 (25%) with disease starting after 60 were demented (Hietanen & Teräväinen, 1988). Another recent study, consistent with these findings, showed that 8.5% of patients with PD starting before 70 years developed dementia, compared with 20.9% of patients with disease onset after 70 years (Mayeux *et al*, 1988). The prevalence of dementia was assessed by retrospective examination of patient records, according to adapted DSM-III criteria, and amounted to 10.9% in the total of 339 patients.

In contrast to suggestions that the PD process differs in young and old patients, our experience of both clinical and pathological characteristics is of a remarkably uniform disease process, particularly with regard to its cerebral distribution and rate of progression (Gibb & Lees, 1988). The rarity of dementia in young-onset patients suggests that the pathology of PD (Lewy bodies and nerve cell loss), in the absence of age-related factors, is insufficient to cause dementia. Dementia therefore appears to be more closely related to age than disease, although age cannot be the only factor because of the higher frequency of dementia in PD compared with the normal ageing population. On taking account of these various prevalence estimates for dementia, the lifetime risk of moderate and severe DSM-III dementia over 65 years is probably 10–20%, or just over twice that of the general population.

Subtypes of dementia

The concept of two types of dementia, cortical and subcortical, is one that evolved in the 1970s; it implies the predominant sites of pathology in two qualitatively different processes. Recently this distinction has been questioned on clinical and pathological grounds. It has even been argued that the dementia of 'subcortical' disorders such as PD and Huntington's disease might not be sufficiently distinct from that of AD to continue employing the term (Whitehouse, 1986). Slowed mental processing has proved difficult to validate, and depression might contribute to the subcortical disturbance. Lastly, pathology is present in subcortical regions in AD, and cortical regions in PD.

Cortical or temporo-parietal dementia

This is most commonly associated with AD and is characterised by severe disruption of memory and thought processes, associated with aphasia, apraxia, agnosia, and spatial disorientation. Mental alertness and motor function are preserved until late in the course of the disease. The amnesia and cortical deficits are believed to result from hippocampal and neocortical pathology, comprising nerve cell loss with accumulations of neurofibrillary tangles and senile plaques. Pathological changes also occur in the nucleus basalis of Meynert, locus coeruleus, raphé nucleus and substantia nigra.

Parkinsonian features have been observed in the later stages of AD, but these are mostly non-specific signs, such as muscular stiffness and slowness of movement. Rest tremor, which is more specific evidence for PD, is reported in only 4% (Sulkava, 1982) and 10% of patients (Mölsä *et al*, 1984). This agrees with pathological data which show that nigral pathology is common in AD, but is usually mild (Gibb *et al*, 1989*a*). The prevalence of PD pathology (Lewy bodies in the substantia nigra) complicating AD is similar to that in the general population (Gibb *et al*, 1989*c*). Other cortical dementias may be accompanied by Parkinsonian features, including cortical Lewy body dementia, corticobasal degeneration (Gibb *et al*, 1989*d*), multi-infarct dementia, rare cases of Pick's disease, and Creutzfeldt–Jakob disease. Parkinsonian disorders with dementia lacking cortical features include Steele–Richardson–Olszewski syndrome, Hallervorden–Spatz disease, communicating hydrocephalus, glial dystrophy, Parkinsonism–dementia complex of Guam, and motor neuron disease. Moderate or severe dementia in PD is not thought to be explained purely by subcortical dementia.

A parallel consideration in idiopathic dementia is the possibility of predicting the neuropathological lesion according to the clinical features. Recent cortical biopsy or autopsy-based studies of patients with idiopathic degenerative dementia found AD in 71–82% (Sulkava *et al*, 1983; Mölsä *et al*, 1985; Neary *et al*, 1986). Other diagnoses were vascular disease, PD, no diagnostic pathology, subcortical gliosis, and normal-pressure hydrocephalus. A recent cortical biopsy study in clinically diagnosed AD has been more optimistic (Martin *et al*, 1987). In the case of dementia complicating PD, the chance of cortical Lewy body dementia is high, and the clinical distinction between cortical Lewy body dementia and AD difficult or impossible.

Subcortical or frontolimbic dementia

Neuropsychological definition of subcortical dementia

Mental slowing in Parkinsonian states has been recognised for many years, one of the first descriptions being that of Naville (1922), who coined the term 'bradyphrenia' to describe the state following encephalitis lethargica. Terms such as 'persistent somnolent psychosis', 'psychic torpor', 'bradypsyche', and 'psychic akinesia' were later used to describe the same phenomenon (see Rogers, 1986; Lees, 1989). Albert *et al* (1974), without reference to this extensive literature, proposed the term 'subcortical dementia' to describe a number of neurobehavioural changes observed in the Steele–Richardson–Olszewski syndrome. This syndrome comprised slowing and inflexibility of thought processes (mental inertia), impaired concentration, and loss of initiative and drive (apathy), associated with impaired ability to manipulate acquired knowledge, lack of imagination, mild forgetfulness, emotional dullness, and a tendency to repetition. As in previous literature, a striking resemblance to the dementia following frontal lobe lesions was noted (Drewe, 1974; Nelson, 1976). The term 'subcortical dementia' was then used to describe the cognitive changes present in other disorders with predominantly subcortical pathology, for example PD (Albert, 1978) and Huntington's chorea (McHugh & Folstein, 1975).

Bradyphrenia is now subsumed under the title of subcortical dementia, where the emphasis lies on mild memory disturbance, mildly disordered thought processes, slow and poorly articulated, quiet speech, apathy, and depression (Benson, 1984). Generally this leads to rather mild intellectual impairments as assessed on a modified mini mental state examination when compared with AD patients at an equivalent functional stage of disability (Mayeux *et al*, 1983). This is similar to the relatively mild nature of the subcortical dementia in Steele–Richardson–Olszewski syndrome (Duvoisin *et al*, 1987). However, qualitative differences in neuropsychological impairments compared with AD cannot be detected using the mini mental state examination (Mayeux *et al*, 1983). AD and PD patients with comparable performances on verbal, visuospatial, and global memory tests show more severe verbal memory disorder in AD, and impaired performance on tests sensitive to frontal lobe dysfunction in PD (Pillon *et al*, 1986; Huber *et al*, 1986; Freedman & Oscar-Berman, 1986).

Bradyphrenia, or subcortical dementia, is recognised clinically by an undue delay in the production of appropriate verbal responses in a co-operative individual without other communication difficulty. The term implies that slowness of verbal responses is due to slowed mental, as distinct from motor, processes. In addition to slowed mental processes, it has been suggested that the neuropyschological deficits underlying bradyphrenia include difficulty in changing mental concepts, and defective attention and motivation (Lees, 1989). However, it has not been possible to show a convincing and consistent reduction in some tests dependent on the speed of mentation. Wilson *et al* (1980) found that high-speed scanning of short-term memory was prolonged in PD, although only in older patients.

Hansch *et al* (1982) examined the long-latency P3 component of the event-related potential in an auditory discrimination task, which is believed to reflect the speed of information processing. The latency of this response in 20 patients with PD was significantly increased compared with controls, and was significantly correlated in a negative fashion with scores on a symbol-digit test. This was interpreted as evidence for bradyphrenia in view of correlation between a test of mental function and the latency of the response. In a study of auditory-evoked potentials in dementia, the N2 and P3 components of the cerebral responses were prolonged in AD and demented patients with PD meeting DSM–III criteria (Goodin & Aminoff, 1986), but not in non-demented patients with PD (Goodin & Aminoff, 1987), so that in the absence of serious cognitive impairment there appears to be no abnormality. The authors pointed out that the P3 response was clearly not specific for bradyphrenia, and could be prolonged in a number of causes of dementia. They noted that the delay in N2 and P3 responses was greater in the demented Parkinsonian patients, and that an additional abnormality was a delay in the N1 component compared with AD.

Evarts *et al* (1981) examined visual and kinaesthetic simple and choice reaction times, and compared these with movement times. There was some correlation between reaction and movement times, but a wide scatter in reaction times, such that they appeared to be independent in some patients. No selective prolongation of choice reaction times was found. In a computer-controlled task, a warning signal was followed by a signal consisting of a light or a high-pitched tone. In the simple reaction-time task, the response (lifting a finger) was made with the dominant hand, and in the choice reaction-time task, the dominant hand was used to respond to the light and the non-dominant hand to the tone (Stern *et al*, 1984). Both simple and choice reaction times were delayed in 39 PD patients. Brown & Marsden (1986) using a left–right discrimination task, both with and without a spatial component, showed no differential impairment of choice reaction time over simple reaction time. Perhaps one of the simplest explanations for the failure of these tests to reveal mental slowing is that they are of the wrong kind, the thought processes being directly driven by the stimulus.

The second neuropsychological defect proposed to underlie bradyphrenia is difficulty in changing mental concepts or sets, a 'set' being defined as "a state of brain activity which predisposes a subject to respond in one way when several alternatives are available" (Flowers & Robertson, 1985). Put another way it is "the ability to reorganize behaviour according to the requirements of a task" (Cools

P 25425

et al, 1984). Cools *et al* (1984) described the inability to reorganise behaviour in PD as a "diminished shifting aptitude", which could be either frontally or basal-ganglia mediated. The Wisconsin Card Sorting Test (WCST) and the Benton Word Fluency Test in early, untreated PD have identified difficulty changing conceptual sets and perseverative errors (Bowen *et al*, 1975; Lees & Smith, 1983). In established PD, Taylor *et al* (1986*a*), also found abnormalities in similar frontal tasks, especially the WCST and Bead-Tapper test (simultaneous manual tasks) and later reported that the WCST, the Rey Auditory Verbal Learning and Bead-Tapper tests were also impaired in nine untreated and 20 treated patients (Taylor *et al*, 1987). Flowers & Robertson (1985) used an odd-man-out discrimination task, and found that Parkinsonian patients had difficulty alternating between two rules on successive trials. The pattern of errors suggested an instability of cognitive set, and not of reasoning ability, perseveration, or distractibility. Taylor *et al* (1987) found that mental processing time on the Trail-Making Test, which tests mental set alternation and excludes motor speed variation, was prolonged in a group (called the poor-response group) showing a declining response to L-dopa (pathological diagnoses in this group are not known), but not in other PD groups. Depression ratings were excluded, but there were no differences in tests of attention and concentration.

Lastly, a number of studies have investigated attention and motivation in patients swinging 'on' and 'off' as a result of L-dopa therapy. An arousal effect of L-dopa has been suggested as the cause of improved mental performance with L-dopa (Loranger *et al*, 1972), and this might be associated with increased speed of thought and absence of perseveration. One of these studies employed the modified Alice Heim test, which incorporates tests of reasoning ability for verbal, numerical, and spatial material (Brown *et al*, 1984). There was no correlation between changes in mental and motor performance; in fact, changes in mental impairment were relatively mild and present only in a proportion of individuals. If one factor was associated with functional impairment, the only real choice was a subjective disturbance of mood and alertness measured during 'off' periods. However, self-rating analogue scales, as used to assess mood and motivation, have been criticised on account of perseveration by the patients (Lees, 1989). These findings are consistent with those of Delis *et al* (1982) and Taylor *et al* (1987), who failed to show alteration in cognitive state dependent on physical state, although importantly the tasks evaluated different functions. Finally, attention and motivation may be an important consideration in six patients with an MPTP-induced Parkinsonian state who showed worse general intellectual function, constructional ability, category naming, and frontal lobe function (Stroop Word-Color test, Part C) compared with eight controls (Stern & Langston, 1985). The two women in the group were depressed.

Other factors of possible relevance to bradyphrenia include the relationship between dopamine and effort in memory processing (Newman *et al*, 1984), 'state-dependent' impairment of memory (Huber *et al*, 1987), and defective planning of movement (Flowers, 1978*b*).

Mechanisms of subcortical dementia

Searches for the pathological substrate of subcortical dementia have included the nucleus basalis, ventral tegmental area, thalamus, and substantia nigra. Neuropsychological deficits now point to a considerable disturbance of frontal lobe function, but how might this arise? Rafal *et al* (1984) postulated that if bradyphrenia resulted from the same dopaminergic imbalance as bradykinesia, then these phenomena should fluctuate in parallel. This question was investigated in six patients with end-of-dose akinesia, who were asssessed with simple measurements of the rate of memory scanning, of shifting attention in the visual field, and the time required for the preparation of a movement. Overall reaction times increased when patients were in the akinetic 'off' state, but without analogous slowing of the cognitive components of these tasks, implying that bradykinesia and bradyphrenia do not result from the same dopaminergic abnormality of the basal ganglia. The absence of slowed mentation accords with the results of other tests of cognitive speed (see above), which unfortunately may not be the most appropriate for evaluating bradyphrenia.

With the benefit of an excellent historical review, Rogers (1986) has outlined the close relationship between bradyphrenia, motor impairment, and depression. Reactive depression as a response to motor disability in the form of apathy and depression is commonly, but not invariably, recognised in those patients with bradyphrenia (Albert *et al*, 1974). Psychological deficits similar to bradyphrenia have also been recognised in depression (Caine, 1981). To what extent is depression related to bradyphrenia in PD? In a study of 30 newly diagnosed patients with PD, not receiving dopaminergic agonists, and 30 patients with primary depressive illness, there was an equivalent slowing of manual responses to a computerised digit symbol substitution test compared with controls (Rogers *et al*, 1987). Rating of motor impairment by the Webster scale and affective impairment by the Hamilton Rating Scale for Depression showed significant differences between each of the PD, depression, and control groups. Matching time, which was a measure of cognitive processing and visual scanning speeds on the tests, was significantly prolonged compared with controls in the nine PD patients with structural disorder on CT scan (cerebral atrophy or infarct). Matching times in the whole PD group were significantly associated with the Hamilton rating. The 18 patients with a normal computerised tomography scan (three did not have a scan) did not even show slowing of the response time (which includes motor speed). Similarly, the 15 more severely depressed patients had a significantly prolonged matching time, and these patients generally had a high Webster score of motor impairment. In both groups some patients were retested after treatment with a dopaminergic agonist or antidepressants, and there seemed to be a relationship between improvement in depression rating and speed of response. The relationship between affect and speed of cognitive processing appeared to be so closely linked that the authors concluded that overlap exists between PD and depressive illness, with the suggestion that the mesocorticolimbic dopaminergic system may be impaired in both states. Evidence was cited for reduced dopamine turnover, assessed by concentration of homovanillic acid in the cerebrospinal fluid, in depressed patients with retardation.

However, some difficulty in identifying damage to the mesocorticolimbic system is apparent from neurochemical data in Steele-Richardson-Olszewski syndrome. In this disorder, frontal lobe deficits are more severe than in PD (Maher *et al*, 1985; Pillon *et al*, 1986), and frontal cortex hypometabolism detected by positron emission tomography is considerable (D'Antona *et al*, 1985). However, dopamine levels in the nucleus accumbens and frontal cortex are not reduced (Ruberg *et al*, 1985; Kish *et al*, 1985), although dopamine receptors are. This contrasts with reductions of frontal cortex dopamine in PD (Scatton *et al*, 1982). In contrast to PD, caudate nucleus dopamine levels are reduced by an equal or greater amount than putamen values. Taylor *et al* (1968*a*) have proposed that frontal lobe dysfunction in PD results primarily from disturbance in caudate outflow as part of the 'complex' loop, comprising a cortico-caudato-nigro-thalamo-cortical circuit (DeLong *et al*, 1983). In PD it is suggested that the defect in the mesocortical system adds an additional non-essential insult to the pre-frontal component of the 'complex' loop.

Depression

The possible relation between depression and bradyphrenia has been discussed. Mild depression occurs as a prodromal feature of PD in as many as a quarter of patients, but occurs at some time during the course of the disease in 30–40% (Mayeux, 1982). This level of depression may be no higher than in other chronic illnesses. For example, Gotham *et al* (1986) found a frequency of 46%, which was similar to that in chronic arthritis. In most cases the depression is believed to be reactive, for example in response to the fear of a progressive degenerative disease. Some, but not all, studies have found correlation with severity of illness and functional disability (Gotham *et al*, 1986). Patients show pessimism, hopelessness, decreased motivation and drive, increased concern over health, and emotional lability. Impaired short-term memory, a feature of primary endogenous depression, is absent (Taylor *et al*, 1986*b*). There is less self-blame, guilt, worthlessness, and self-destructive feeling compared with endogenous depression (Gotham *et al*, 1986; Taylor *et al*, 1986*b*). Endogenous mechanisms seem likely in the few patients who have substantial depression in the prodromal phase or depression associated with psychotic features.

Basic pathology of Parkinson's disease

The hallmark of PD was first described by Friederich Lewy in 1912 as an eosinophilic neuronal inclusion in the nucleus basalis and dorsal vagal nucleus. Tretiakoff (1919) described a similar inclusion body in the substantia nigra, and suggested that it was relatively specific for PD. This has remained a matter of doubt until recently, when the Lewy body has been demonstrated in a proportion of remaining pigmented neurons of the substantia nigra in every case of PD (Gibbs & Lees, 1989). Pathological diagnostic criteria for PD can now be proposed, the first of which is the invariable presence of the Lewy body in two unilateral sections of substantia nigra. The second is a greater than 60% loss of nigral neurons. The third is the exclusion of striatonigral degeneration, Steele-Richardson-Olszewski syndrome, and other Parkinsonian disorders associated with neuronal loss in the substantia nigra. Lewy bodies also occur in the substantia nigra in as many as 10% of elderly healthy controls (incidental Lewy body disease), believed to have pre-clinical PD, and may thus be an incidental finding in other Parkinsonian disorders. In addition, they are an inconsistent feature in a variety of uncommon disorders (Gibb, 1986).

The Lewy body lies within the cytoplasm of nerve cells, in nerve cell processes, or is occasionally free in neuropil; it is recognised by its characteristic eosinophilic staining and surrounding halo. Ultrastructurally, a large part of it comprises filamentous material, roughly similar to neurofilament. Other cytoskeletal components have also been identified immunocytochemically (Dickson *et al*, 1985), and still other components, principally those of the dense and variable 'core', have not been identified. Lewy bodies have a specific and consistent distribution in the nervous system, their other principal locations being the locus coeruleus, raphé nuclei, thalamus, nucleus basalis, cerebral cortex, and the entire autonomic nervous system, including the hypothalamus, dorsal vagal nucleus, intermediolateral columns, sympathetic ganglia, and parasympathetic myenteric plexi. Lewy bodies are not found in these different parts of the nervous system without also being present in the substantia nigra and locus coeruleus, although their occurrence in anterior horn cells, which is restricted to rare cases of motor neuron disease (Hirano *et al*, 1984), is the single exception to this rule.

In PD, Lewy bodies are almost invariably found in the nucleus basalis, dorsal vagal nucleus, autonomic ganglia, and hypothalamus, and in a third of cases in the cerebral cortex (Gibb & Lees, 1987). Neuronal loss has been demonstrated for most of the locations in which Lewy bodies are found. Additionally, neuronal loss in PD does not occur without Lewy bodies, so they are considered an early marker of neuronal cell degeneration, when neuronal loss is not apparent (Langston & Forno, 1978). The generalised but specific distribution of Lewy bodies in PD, the identical distribution of Lewy bodies in patients presenting with autonomic failure or dementia, and the occurrence of Lewy bodies in a population with insufficient nigral neuronal loss to cause symptoms, suggests a single disease entity with varying manifestations, prompting the inclusive term 'idiopathic Lewy body disease' (Gibb & Lees, 1988*b*).

In the context of the present discussion, the comparatively large size of the pre-clinical PD population, the prevalence of which rose from approximately 2% in the 1950s to 10% in the '80s, emphasises three points (Gibb & Lees, 1988*b*). First, there is a critical threshold for symptoms, which depends on the degree of nigral neuronal loss (estimated at 60%), striatal dopamine loss (estimated at 80%), and compensatory post-synaptic dopaminergic hypersensitivity. Second, the degree of nigral neuronal loss at death is always moderate at 75–80%, and never extreme. Third, the much lower prevalence of symptomatic compared with pre-symptomatic PD suggests a long pre-clinical period, and a slow rate of nigral destruction. This moderate neuronal loss is also seen in the ventral tegmental area (estimated at 40–64%, Bogerts *et al*, 1983), the locus coeruleus (estimated at 75–80%, Mann *et al*, 1983), and the nucleus basalis (estimated at 20–80%, Ezrin-Waters & Resch, 1986), emphasising that critical thresholds are likely to determine whether symptoms will result from damage at other sites.

The pathology of dementia in Parkinson's disease

Neuropathological and biochemical research into the cause of dementia in PD can be divided into three main phases: firstly, the identification of Alzheimer-type neocortical pathology; secondly, the discovery of cell loss in the nucleus basalis; and thirdly, the recognition of Lewy bodies in the cerebral cortex. Each of these lesions has received support as a principal cause of dementia, but there is no clear consensus as to their relative contributions. Initially, the direction of research was influenced by the abnormalities found in AD.

Alzheimer's disease and Alzheimer pathology

The principal lesions associated with the dementia of AD comprise senile neuritic plaques, neurofibrillary tangles, neuronal loss, and granulovacuolar degeneration, predominantly in hippocampal pyramidal cells and neocortex. These changes are also found in elderly persons who are not demented (Quinn *et al*, 1986), and in other disorders such as pugilistic encephalopathy, Parkinsonism–dementia complex of Guam, and Hallervorden–Spatz disease. Nevertheless, they are more severe in AD compared with the elderly, non-demented population, and their distribution especially involves the neocortex rather than the hippocampal region alone.

In the 1960s it was proposed that the number of plaques and tangles correlated approximately with the severity of dementia (Corsellis, 1962; Roth *et al*, 1966). Blessed *et al* (1968) found a mean plaque count of 20.8 in 60 fields (1.3 mm in diameter, 25 μm section thickness) from 12 cortical areas, compared with a count of 5.1 in controls. Tomlinson *et al* (1968, 1970) stated that large numbers of evenly distributed plaques (more than 18 per 'low-power field'), neurofibrillary tangles throughout the cortex, or numerous hippocampal pyramidal cells showing granulovacuolar degeneration occurred only in demented elderly persons, and not in normal elderly persons.

Concern that the correlation between dementia scores and plaques was imperfect (Blessed *et al*, 1968; Tomlinson *et al*, 1970; Wilcock & Esiri, 1982) turned attention to the possibility that tangles serve as a more accurate histological arbiter of disease severity. Ball (1977) derived an adjusted tangle index and, like previous authors (Tomlinson *et al*, 1970; Dayan, 1970), found greater numbers of tangles in the hippocampus of demented subjects compared with a control population. Wilcock & Esiri (1982) examined the relationship of plaques and tangles in different lobes of the brain and found that tangles, but not plaques, were significantly correlated with dementia, especially in superior and middle temporal gyri. Tangles were also more easily quantified, as they are smaller and of more uniform size.

Despite these developments, the most appropriate histological parameter of AD is still disputed. Ball *et al* (1985) found that in every case diagnosed clinically as uncomplicated AD, the hippocampus contained (a) at least 20 tangle-bearing neurons per mm^3 (the adjusted tangle index), and/or (b) at least 55 nucleolated neurons per mm^3 showing granulovacuolar degeneration, and/or (c) a population of less than 5600 nucleolated nerve cells per mm^3. In contrast, most investigators consider that the extent of neocortical pathology most efficiently distinguishes between normal ageing and dementia, but precise neuropathological criteria for the diagnosis of dementia (e.g. number of tangles in temporal cortex) are difficult to establish, partly because of the effect of age on counts of neocortical plaques and tangles (Mann *et al*, 1984). Older compared with younger patients with AD show fewer tangles and plaques (Rossor *et al*, 1984).

Minimum criteria for histological diagnosis have been suggested (Khachaturian, 1985). The minimum number of areas to be sampled include three regions of neocortex, the amygdala, and the hippocampus. Other causes of dementia are excluded. In any microscopic field in the neocortex encompassing 1 mm^2 (magnification ×200) there should be more than two to five plaques and tangles in patients younger than 50 years, more than eight plaques between ages 50–65, more than ten plaques between ages 66 and 75, and more than 15 plaques over age 75 years. Tangles are often present, but may be absent over 75 years.

Additional pathological findings in AD include loss of cortical neurons and reduced brain weights. Cell loss is restricted to a small subpopulation of large neurons, which are reduced by 40–50% in frontal and temporal cortex (Terry *et al*, 1981; Mountjoy *et al*, 1983). Reduction of brain weight is usually slight, but younger patients show atrophy, particularly in the anterior temporal lobes and other cortical association areas. Lastly, granulovacuolar degeneration usually affects more than 9% of hippocampal pyramidal cells (Tomlinson *et al*, 1970; Ball, 1977, 1978).

The level of ChAT, the biosynthetic enzyme for acetylcholine, is decreased in the cortex (Davies & Maloney, 1976; Perry *et al*, 1977*a*,*b*; White *et al*, 1977) broadly in line with the severity of dementia and the number of plaques (Perry *et al*, 1978) and tangles (Wilcock *et al*, 1982). ChAT is also reduced in the nucleus basalis (Davies, 1979; Reisine *et al*, 1977; Rossor *et al*, 1982; Candy *et al*, 1983*a*), a finding of particular interest, as this structure contains cholinergic neurons projecting to the cortex. In addition Whitehouse *et al* (1981, 1982*a*,*b*) demonstrated that nucleus basalis cell numbers were reduced by a mean of 79%. Most other investigators found less impressive reductions of 35–76%, which approximately match the cortical cholinergic deficit (Arendt *et al*, 1983; Tagliavini & Pilleri, 1983; Wilcock *et al*, 1983; Candy *et al*, 1983*a*), although not in all studies (Perry *et al*, 1983*a*). This finding is now fundamental to the cholinergic hypothesis of dementia.

The primary site of neuronal damage is unknown, although ChAT activity seems to be reduced by over 90% in the nucleus basalis, whereas the loss of cholinergic perikarya is only 35%, suggesting a primary degeneration of axons projecting to the cortex, with secondary loss of perikarya (Candy *et al*, 1983*b*). Cortical abnormalities may induce retrograde degeneration of projections from the nucleus basalis, as well as other areas, such as the locus coeruleus and raphé nuclei (Perry, 1985; Mann *et al*, 1985).

A recent study of early-onset AD showed that acetylcholine synthesis in temporal cortex biopsy specimens correlated with cognitive impairment, suggesting that a deficit in the pre-synaptic cholinergic system occurs relatively early in the disease, and that post-synaptic changes in cortical neurons might be a secondary effect not so closely linked to the defect (Francis *et al*, 1985).

In addition to cell loss in the nucleus basalis, some of the remaining neurons contain tangles. Other subcortical nuclei showing cell loss and tangles, particularly in young-onset cases, are the locus coeruleus (Mann *et al*, 1983), raphé nuclei (Yamamoto & Hirano, 1985), and to a lesser extent the ventral tegmental area (Mann *et al*, 1987) and substantia nigra (Tabaton *et al*, 1985; Rinne *et al*, 1986; Gibb *et al*, 1989*a*). There are consequent reductions of noradrenaline and serotonin in the cortex, and of dopamine in the caudate nucleus and putamen.

Alzheimer's disease and Parkinson's disease

The discovery of correlations between plaques and tangles and the dementia of AD led to the description of cell loss, plaques, and tangles in the neocortex, and granulovacuolar degeneration in the hippocampus of patients with PD and dementia (Alvord *et al*, 1974; Hakim & Mathieson, 1979; Boller *et al*, 1980; Ditter & Mirra, 1987; Leverenz & Sumi, 1986). This carried the implication that an increased prevalence of AD explained the dementia of PD. However, such changes received limited quantification, and formal psychological evaluations were not arranged prospectively, the mental status being estimated from information obtained from clinical records. Nevertheless some authors have continued to support the view that dementia is caused by coexistent AD (Cummings *et al*, 1980; Boller, 1980), while others were critical of the methodology in these early studies, and believed they overestimated the severity of the neocortical changes (Mann & Yates, 1983; Ball, 1984; Perry *et al*, 1985).

Cortical atrophy has been described in typical (Selby, 1968) and 'atypical' cases (Sroka *et al*, 1981) of PD, the degree of which has been linked to age and disease duration (Jellinger & Riederer, 1984). However, in most cases brain weights are within the normal range. A study of computerised tomography scans found that ventricular enlargement, but not cortical atrophy, correlated with mental change (Portin *et al*, 1984).

Some early studies in which mental function was not examined failed to find significant depletions of cortical ChAT (Lloyd *et al*, 1975; Reisine *et al*, 1977). Later Ruberg *et al* (1982) found a fall in ChAT levels in frontal cortex of about 50%, and a rise in muscarinic cholinergic receptor density that correlated with the degree of dementia assessed retrospectively. Parallel observations were made by Perry *et al* (1983*a*). It was also suggested that a fall in ChAT concentration preceding the onset of dementia might explain the tendency for many patients to suffer reversible confusional states, especially when prescribed cholinergic antagonists (DeSmet *et al*, 1982; Dubois *et al*, 1983). Anticholinergic drugs were known to have adverse effects on memory in PD (Sadeh *et al*, 1982), but the more specific proposal of Dubois *et al* (1983) was that subthreshold doses of an anticholinergic, which would have no effect on controls, would have deleterious effects on intellectually normal Parkinsonian patients already depleted of cortical acetylcholine.

This was tested in 32 Parkinsonian patients and 32 controls matched in groups for age, education, and intellectual state (Dubois *et al*, 1987). In a double-blind, single-cross-over study, the patients were given scopolamine (0.25 mg) or placebo on day 1, followed by the second of the medications on day 2. In control subjects the anticholinergic had no effect on five tests of memory, but the patients failed on two of the tests that required that meaningless drawings were recognised, results ascribed to possible frontal lobe dysfunction.

Whitehouse *et al* (1983) identified nucleus basalis cell loss in PD, with the greatest depletion occurring in patients with dementia. In another small series, cell loss ranged from 30% to 68%, but could not be related to mental state (Tagliavini *et al*, 1984). Other investigators recorded depletions of 58–77% in patients with dementia (Arendt *et al*, 1983; Rogers *et al*, 1985). Whitehouse *et al* (1983) also reported that in PD, neuronal loss occurred throughout the magnocellular basal forebrain system, the nucleus basalis, medial septal nucleus, and nucleus of the diagonal band of Broca, but in the latter two sites neurons were intact in non-demented patients. A limited statistical analysis showed 74% loss in nucleus basalis in demented cases compared with non-Parkinsonian controls. Taken with the publications on Alzheimer pathology, this would imply that dementia might be due to tangles and plaques in the cortex and neuronal degeneration in the nucleus basalis, either alone or in combination. The strength of evidence favouring the cholinergic hypothesis of dementia and the finding of cortical ChAT depletion in AD and PD encouraged the view that the cause of these dementias was identical.

First suspicions that the analogy with AD (nucleus basalis neuronal loss and cortical Alzheimer pathology) might not be so close came from Gaspar & Gray (1984). They confirmed significantly greater (60%) nucleus basalis cell loss in demented patients compared with that in non-demented patients (32% loss), where mental status was examined retrospectively. The 46% mean loss was lower than obtained in previous studies. ChAT activities were severely reduced in five patients and appeared to correlate with dementia, but could not be linked to cortical tangles and plaques, suggesting that in some patients degeneration of the main ascending cortical input from the nucleus basalis occurred without cortical Alzheimer pathology.

In another study, of 11 patients whose mental state was not examined, eight had 60% depletion of nucleus basalis neurons, but without significant AD lesions (Nakano & Hirano, 1984). A study of 14 PD cases included three that had pathological features sufficient for a diagnosis of AD (Perry *et al*, 1985). In the remainder, tangles were absent from the cortex, and senile plaques lay within the previously established normal range of 0–14/1.3 mm^3. Seven of these 11 patients were mentally impaired, and their ChAT levels were reduced by 66–78%, in all four cortical lobes, with less severely reduced acetylcholinesterase. The ChAT activities correlated with mental impairment, assessed by tests of memory and information, and also with neuronal loss in the nucleus basalis, which amounted to 72% in the mentally impaired subgroup. It did not correlate with neocortical tangle or plaque formation.

Ball (1984) reviewed the data presented by Hakim & Mathieson (1979) concerning the high frequency of Alzheimer pathology in PD, and noted that although Alzheimer pathology was more common in PD there was no statement concerning a possible correlation between the severity of the pathological change and mental state. Reworking of the data using Student's *t*-test showed no significant difference between the number of tangles in 19 subjects with dementia when compared with the 15 without dementia.

Overemphasis and incorrect interpretation of Alzheimer pathology has probably been a factor encouraging many studies to propose that AD and PD are in some way associated. While AD and PD must occasionally coexist, there are virtually no studies which discount a specific association. On occasions Alzheimer pathology and Lewy body neuronal degeneration are clearly dissociated, and can be separately linked with dementia. In AD, neurofibrillary tangle/neuronal degeneration in the nucleus basalis, cortical Alzheimer pathology, and cortical ChAT depletion are associated with dementia; in PD Lewy-body/neuronal degeneration in the nucleus basalis is associated with cortical ChAT depletion, cortical Lewy bodies and dementia. It is therefore a statistical question whether AD and PD coexist more often than chance would allow. In this regard, purely clinical studies are meaningless, because of the inaccuracies inherent in the clinical diagnosis of AD and PD, as reviewed above. Most pathological studies have quantified cortical tangle and plaque pathology in patients with PD, but this approach is also of dubious accuracy in the absence of well defined quantitative thresholds for the pathological diagnosis of AD. An alternative strategy is to study the number of patients with pre-symptomatic PD among a population with AD, and to compare this with controls.

Jellinger & Riederer (1984) reported 128 cases of senile dementia of Alzheimer type and 68 cases of AD, with mean ages of 80.7 years and 65.4 years respectively. The combined mean age was 75.4 years, which compared with a mean of 74.3 years in 180 control patients. Examination of locus coeruleus and substantia nigra showed Lewy bodies in 15–22% of the AD cases and in 10–16% of controls, figures which are not significantly different. In another study, 12 (7.8%) of 273 controls dying over 60 years showed nigral Lewy bodies compared with 14 (14.0%) of 100 cases of AD, with mild nigral cell loss (Gibb *et al*, 1989*c*). The patients with AD and nigral Lewy bodies showed fewer cortical tangles and plaques, but the same cortical ChAT activities, suggesting that Lewy body degeneration in the nucleus basalis contributed to the cholinergic depletion and therefore to the dementia, but not to the cortical Alzheimer pathology. A slightly higher prevalence of Lewy bodies in the patients with AD was probably due to selection into the study of pre-symptomatic or borderline cases of AD, in which dementia was precipitated by coexistent Lewy body pathology.

Lastly, Down's syndrome, which is frequently complicated by premature AD (Godridge *et al*, 1987), is not associated with Lewy body pathology. In general, there does not therefore appear to be evidence for a link between the fundamental pathological processes underlying AD and PD, although one or two exceptions are discussed below. Dementia in PD appears to be commonly associated with Alzheimer pathology because of the dual insult, principally to the innominato-cortical system and cerebral cortex.

At this point we can conclude that dementia in PD is associated with Lewy-body/neuronal degeneration in the nucleus basalis, with or without AD pathology, of a degree that is either pre-symptomatic or symptomatic for dementia. What other pathological lesions are associated with dementia?

Cortical Lewy bodies

Forno (1969) found Lewy bodies in the cerebral cortex in six out of 50 persons (12%) with incidental nigral Lewy bodies (pre-clinical PD), and they can be found in the parahippocampus or temporal cortex in about one third of patients with PD (Gibb & Lees, 1987). Multiple cortical Lewy bodies associated with dementia were first described in Hallervorden–Spatz disease (Helfand, 1935), and later in patients with idiopathic PD (Okazaki *et al*, 1961). Of 23 'idiopathic' cases reported by Japanese neuropathologists, the mean age at onset was 56.7 years (range 26–72 years) (Gibb *et al*, 1987). It was 59.7 years (range 27–74 years) in 17 additional cases (Sima *et al*, 1986; Clark *et al*, 1986; Dickson *et al*, 1987; Gibb *et al*, 1987), although Lewy bodies were restricted to the hippocampus in some (Dickson *et al*, 1987, cases 1, 3, and 5). Paranoid delusions, visual hallucinations, aphasia, apraxia, agnosia, and spatial disorientation were common. Twelve of the series of 23 had considerable cortical Alzheimer pathology, possibly of sufficient severity for AD, although in some other cases it was mild or absent (Gibb *et al*, 1987). It was described as mild or absent in seven of the 17 patients (41%) reported more recently (Sima *et al*, 1986; Clark *et al*, 1986; Dickson *et al*, 1987; Gibb *et al*, 1987).

The occurrence of substantial Alzheimer pathology in 19 of 40 reported cases (48%) argues in favour of Alzheimer pathology contributing to the dementia in some patients. While the expected prevalence of AD would be well below 10%, around a mean age of 58 years, the frequency of Alzheimer pathology in the hippocampus is 40.0% in the 50–59-year age group, 50.0% at 60–69 years, and 57.1% at 70–79 years, figures collated by combining data from seven studies (Gibb, 1987). If the severity of Alzheimer pathology is not formally quantified, there is probably considerable scope for implying a diagnosis of AD based on a subjective assessment of tangle and plaque numbers. Enthusiastic assessment of pathology relevant to the aetiology of dementia is likely to influence this subjective and poorly defined diagnostic threshold. Despite these arguments, it is clear that dementia in PD can be associated with cortical Lewy bodies alone, or with additional Alzheimer pathology, so that Alzheimer changes are not an obligatory factor. Indeed, the general rule in cases of Hallervorden–Spatz disease with Lewy bodies is that Alzheimer pathology is absent.

I have implied that all patients with cortical Lewy body dementia have PD, but this is not the case. The inclusive pathological term 'idiopathic Lewy body disease' describes the characteristic distribution of Lewy bodies and neuronal degeneration in the nervous system. In some cases the process causing dementia progresses more rapidly and causes symptoms at a time when nigral cell loss is equivalent to the pre-symptomatic stage of PD (less than 60%). Parkinsonian features may or may not emerge during the course of the dementia; if they do not, the condition remains indistinguishable from AD (Gibb *et al*, 1989*b*). Cortical Lewy bodies are not usually associated with obvious cell loss, but a degree of neuronal degeneration would be consistent with their effects elsewhere in the nervous system.

The term 'diffuse Lewy body disease' was introduced to describe patients with cortical Lewy bodies and dementia (Kono *et al*, 1976; Yoshimura *et al*, 1980), but this term is inappropriate because the distribution of the disease is no more widespread than usual, and Lewy bodies do not occur 'diffusely' in the nervous system. It is the emphasis and severity of the Lewy body disease in different parts of the nervous system that varies. Lewy bodies in the cortex are found only in certain neurons located mostly in the deeper laminae, and they do not occur in the hippocampus. They have a consistent propensity to occur in the temporal and frontal cortex, insular cortex, and cingulate gyrus.

Occasional cortical Lewy bodies are often found in non-demented Parkinsonian patients, moderate numbers are found in a few patients, approximately 5–7% (Yoshimura, 1983), and numerous Lewy bodies in fewer than 2%. Despite the high frequency of cortical Lewy bodies in PD, our experience would suggest that not more than 5% of patients with idiopathic Lewy body disease develop dementia, with or without Parkinsonian features, wholly or partly related to cortical Lewy bodies. There is a spectrum of cortical disease, and there are no convincing reasons for considering cortical Lewy body disease/dementia pathologically distinct from PD. Factors that may account for the relatively recent recognition of cortical Lewy bodies include the subcortical location of most pathology in PD, the pursuit of Alzheimer changes in early studies of dementia, and the less conspicuous histological nature of cortical Lewy bodies. In addition, numerous other cortical neurons lacking Lewy bodies often show less well defined, non-staining, pale inclusions (Gibb *et al*, 1987). Recognition of cortical Lewy bodies might have led to alternative interpretations in some recent studies (Heilig *et al*, 1985; Chui *et al*, 1986; Leverenz & Sumi, 1986; Ditter & Mirra, 1987).

The functional consequence of cortical Lewy bodies is unknown. In AD there is a consistent reduction in cortical somatostatin (Davies *et al*, 1980), which may result from degeneration of intrinsic somatostatin neurons (Beal *et al*, 1986). Demented Parkinsonian patients also show reduced cortical somatostatin (Epelbaum *et al*, 1983) and cerebrospinal fluid somatostatin-like immunoreactivity (Jolkkonen *et al*, 1986). Some cortical Lewy bodies develop in somatostatin-containing neurons.

Having attempted to discount a specific pathological association between AD and PD, there are eight patients recorded in whom Lewy bodies and AD pathology coexisted at such a young age, less than 60 years, that their association is difficult to dismiss as one of chance. They were aged 22–47 years at onset of their Parkinsonian disorder or dementia, and aged 28–56 years at the time of death (Kosaka *et al*, 1973; Kayano *et al*, 1980; Okeda *et al*, 1982; Gibb *et al*, 1987, case 2; Popovitch *et al*, 1987; Delisle *et al*, 1987; Gibb *et al*, 1989*c*, two cases). Five of these cases had fairly florid cerebral involvement with both Lewy body and Alzheimer pathology. The case of Popovitch *et al* (1987) was a 28-year-old mentally retarded man who developed dementia from age 22 years, followed by muscular rigidity and a quadriparetic flexion posture before death. A twin brother was healthy, but "both maternal parents had histories of mental illness". A CT scan at 27 years showed "ventricular dilatation associated with cerebral atrophy" and autopsy showed many cortical and subcortical tangles, an unstated number of cortical Lewy bodies, and brainstem Lewy bodies also. A patient aged 49 years, described by Delisle *et al* (1987), developed motor neuron disease at the age of 36, followed by extrapyramidal rigidity and dementia a few months before death. There were moderate numbers of cortical Lewy bodies, with mild Alzheimer pathology, and loss of anterior horn motor neurons, and Lewy bodies in the spinal cord, although not in surviving motor neurons. These few cases should not detract from the weight of evidence that argues against a specific association between Lewy body disease and Alzheimer pathology in the majority of patients.

The locus coeruleus and dementia

Other nuclear groups that have been investigated in relation to dementia include the locus coeruleus, where neuronal loss is reportedly greater in patients with dementia (Gaspar & Gray, 1984), as are the reductions in noradrenaline (Cash *et al*, 1987). However, cortical noradrenaline levels show equivalent reductions in demented and non-demented patients, or significant reductions in demented patients, that do not correlate with the severity of the dementia (Francis *et al*, 1985). When interpreting the effects of neuronal degeneration in the locus coeruleus, the possibility of coexistent Alzheimer pathology, as for the nucleus basalis, needs to be considered.

The substantia nigra and dementia

Rising prevalence rates of dementia with increasing disease duration aroused suspicion that dementia might be closely linked to progressive motor impairment, or even to long-term L-dopa therapy (Sweet *et al*, 1976; Rajput *et al*, 1984). It was suggested that loss of nigrostriatal activity, the cause of increasing motor disability, might contribute to dementia (Ball, 1984). It is also true that improvement in some cognitive functions often follows the start of L-dopa therapy (Portin *et al*, 1984), although this has been attributed to its awakening effect. One careful examination of the relationship between intellectual performance and motor function involved a group of patients experiencing severe and rapid fluctuations in motor disability between phases of extreme immobility and mobility (Brown *et al*, 1984). There were no significant alterations in intellectual performance assessed using the modified Alice Heim test, but minor fluctuations were thought to be due to alterations in mood and alertness. Lastly, histological studies have not been able to correlate the degree of nigral neuronal loss with dementia (Gaspar & Gray, 1984). Any apparent ill-effect of L-dopa is thus likely to be related to age and the duration of the disease, which are related to the prevalence of dementia.

Ventral tegmental area and dementia

Impaired function of the ascending dopaminergic mesocorticolimbic projection is widely believed to contribute to the frontal lobe dysfunctions contributing to dementia (but see above), but is not thought to be important in severe dementia.

Summary

In this review I have identified the following main points.

(a) Neuropsychological deficits described in PD do not signify widespread cortical pathology, but frontal lobe deficits imply disruption of caudate nucleus outflow.
(b) The prevalence of dementia is approximately 10–20%, which is twice that in the general population.
(c) Dementia is rare in young-onset PD, despite long survival, and is therefore more closely related to age than to PD.
(d) Important characteristics of Lewy body disease are slow rates and modest degrees of neuronal loss. There are thresholds of neurochemical depletion corresponding to the onset of symptoms, which are functionally important and most readily appreciated in the substantia nigra.
(e) The three major pathologies associated with dementia are AD, Lewy body neuronal degeneration in the nucleus basalis, and cortical Lewy bodies.
(f) There is no concrete evidence favouring a greater than chance association between AD and PD.

What then is the pathological substratum for dementia? Of the three pathologies cited, only AD is more closely related to age than to disease. One other possible factor is an age-related reduction in numbers or function of nucleus basalis neurons (McGeer *et al*, 1984), although this is not well substantiated. There is no evidence that Lewy body disease shows a different spectrum at different ages. Lewy-body/neuronal degeneration in the nucleus basalis or cortex is no more severe in older-onset patients. Tagliavini *et al* (1984) observed in PD that nucleus basalis depletion does not vary with age; and the mean age of patients presenting with cortical Lewy body dementia is similar to the mean presenting age for PD. The threshold level at which symptoms arise as a result of nucleus basalis damage is unknown, but nerve cell depletions between 20% and 50% are quoted for non-demented patients, and between 40% and 80% for demented patients (Ezrin-Waters & Resch, 1986). The isolated cholinergic depletion that results may cause amnesia, but is probably an insufficient cause for dementia. Additional cortical pathology is presumably mandatory.

The rare occurrence of dementia in young-onset PD indicates that nucleus basalis degeneration, with or without cortical Lewy bodies, is not usually severe enough to cause dementia. Cortical Lewy body pathology is probably sufficiently severe to precipitate dementia in very few patients, for example less than 2%, which is the prevalence figure for dementia in young-onset PD. In an additional 5–7% of patients over 65 years, dementia is provoked by moderate to severe AD, as in the general population.

An additional 3–13% prevalence is required to tally with the 10–20% prevalence of dementia in PD. This might be derived from: (a) about 7% of patients with pre-symptomatic Alzheimer pathology and Lewy-body/neuronal degeneration in the nucleus basalis; (b) about 3% of patients with pre-symptomatic cortical Lewy body disease and Lewy-body/neuronal degeneration in the nucleus basalis; and (c) up to 5% of patients in whom dementia is associated with a combination of cortical Alzheimer pathology, nucleus basalis depletion, and cortical Lewy body disease. However, in the latter situation cortical Lewy bodies are mostly of little significance in view of their usually small numbers, and their presence should not be interpreted as a culpable factor for the dementia.

There are a number of areas of interest in the further elucidation of dementia in PD. Sadly the scope for specific therapy is limited. More information is required on the spectrum of nucleus basalis damage in PD, at different ages of onset, and different disease durations. Accurate data on the chemical and neuronal depletions in the nucleus basalis are required when additional pathologies, such as AD, are present. Greater knowledge of the neurochemical consequences of cortical Lewy bodies and AD could conceivably reveal specific therapeutic approaches. Identification of more young patients with Alzheimer and Lewy body pathology, especially if familial, may unravel pathogenetic mechanisms. Ideally the material to answer such questions should be selected from the countless individuals with dementia or Parkinsonian disorders, who should be prospectively evaluated clinically, as well as pathologically.

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Comment

Community Care and the Difficult and Offender Patient

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Concern has been growing about a cyclical pattern or 'periodicity' in mental health care over the past 300 years, in which large-scale policy decisions have been made, and then reversed, paying little attention to the particular needs of differing patient groups. Turner (1985) drew attention to the reckless course followed by psychiatry, and how the "discipline that has lost its way" (*Lancet*, 1985) may have done so owing to a poor grasp of its past history. In the movement towards community care, 'difficult' or the so-called 'unrewarding' (to use Scott's (1970) term) patients are a particularly vulnerable group (Aviram & Segal, 1973; Bachrach, 1980). Increasingly, community services are compelled to cater for less disturbed patients through being selective about whom they will accept. To a degree, forensic services on both sides of the Atlantic have partially filled the gap so created in service provision. For this and other reasons, it is difficult to make a general statement about the effectiveness of deinstitutionalisation and community care. To be more specific, there are basic conceptual difficulties in defining continuity of care and identifying subgroups for which it has different implications (Bachrach, 1981), and there are major methodological difficulties impeding an analysis of such a diffuse and fragmented provision. Scull's (1984) description of the overnight abolition of state facilities for juvenile offenders in Massachusetts in the US between 1969 and 1973 points to the impossibility of making a comparison 'before and after', when so much dissolution and decentralisation of services has occurred (see also Jones, 1982). A few model alternatives were described soon after the closures, and Bachrach (1980) has written about the dangers of generalising from model programmes, highlighting the differences between demonstration efforts and reality. It is proposed here that the difficult and offender population might act as a 'litmus paper' for the efficiency, or otherwise, of community care in general.

Over ten years ago in the UK, attention was drawn to the problems posed to hospitals and prisons by the difficult and chronic behaviourally disturbed patients, previously absorbed by the older asylums (Bowden, 1977; Bluglass, 1978; Orr, 1978). Difficulties within the originating family often leads to an early rejection from their family home (Grad & Sainsbury, 1968; Brown *et al*, 1972; Miles, 1981). These problem patients wander the streets, and if their behaviour becomes criminalised they may enter the prison system. Bachrach (1980), Caton (1981) and Lamb (1982) describe a rising tide of chronic behaviourally disturbed individuals who are young, single, occasionally schizophrenic, and often personality disordered. It could be argued that the closure of mental hospitals and the restricted admission to the smaller psychiatric units has led, *inter alia*, to the substitution of inner-city decay for back-ward neglect (Aviram & Segal, 1973; Sands, 1984). The open-door policy developed partly as a consequence of the 'pharmacotherapy era' and enlightened voluntary admission practices, but the situation is more complex than this. By examining the process in greater detail, the influence of, for instance, the neuroleptics can be put into proper perspective – the 'revolutionary treatment methods' can be demythologised, revealing the reality of community care (Dunham, 1965; Scull, 1984). The advantages of the neuroleptics, advanced by the policy makers as allowing deinstitutionalisation, might be seen as a rationalisation for the uncomfortable fact that social policy is strongly influenced by fiscal reality (Scull, 1984; Turner, 1985; Friedman, 1985). Scull (1984) has written provocatively on this matter, and draws our attention particularly to policy decisions behind what he calls 'decarceration'. He points out that the political right found it expedient to close psychiatric hospitals for financial reasons, and the political left encouraged it for 'libertarian reasons'. The 19th century saw the building of institutions and the subsequent neglect of the inmates, and the 20th century saw the dismantling of the institutions and the subsequent neglect of the released patients. Psychiatry, it appears, has not 'taken its own history'.

Historical context

In the 18th century the mentally disordered were a 'submerged problem' (Jones, 1972). They constituted no specific group, and if they offended they were judged by the penal law: if they were poor and dependent they were dealt with by the poor law, and if they wandered outside their 'catchment area' they were dealt with by the vagrancy laws. This blurring of boundaries between the indigent, the criminal, and the mentally ill, commented upon initially by Penrose (1939), and more recently by Steadman (1985), may still be with us.

At the turn of the 19th century, industrialisation and the emergence of a capitalist society effectively destroyed the socio-cultural homeostasis of a more rural community, increasing the proportion of the socially vulnerable. The population of London doubled between 1750 and 1770, and the precipitate drop in the mean age of the populace led to the labour market being flooded with the young, and with unemployment came an explosion in crime. Hughes (1987) provides an exhaustive account of how England temporarily solved the problem by colonising Australia and establishing penal settlements. It is possible that the psychologically vulnerable (the 'Johnny Raws') made up a sizeable population of these unhappy convicts. Foucault (1961) and Scull (1979) ascribed the building of asylums to a growing need for the social control of what became known as 'the mob'. Bentham's (1843) ***Panopticon*** provided one model for the re-creation of a vigilance and observation felt to be lost, but necessary in the changing society.

The dissolution of the 'community' gave way at the start of the 19th century to a period of institutionalisation. In the words of Dorothea Dix, an advocate of the mentally ill in the US in the 19th century, 'no fact is better established in all hospital annals than this; that it is cheaper to take charge of the insane in the curative institution than to support them elsewhere for life' (quoted by Deutsch, 1949). Grob (1966, 1973) ascribes the growth of the hospital movement, also in the US, to social, cultural, and economic factors related to the breakdown of provisions for informal care. So one must take care when advocating the return of patients to a 'depleted' community, unless adequate care is taken to 'rebuild' that community. Proper funding is the cement of this rebuilding.

Movement towards the community

Conditions were difficult to maintain in the asylums, but things were fairly quiet for the greater part of the 20th century in the (renamed) mental hospitals, conspicuous by their 'gigantic water tower and chimney combined, rising unmistakably and daunting in the countryside' as Enoch Powell (1961) saw them. The Ely Hospital inquiry in 1967 in the UK drew public attention to one unacceptable face of institutionalisation, and led to several other inquiries from which allegations were proved and prosecutions followed (Martin, 1984). The conditions of the mentally handicapped in-patient population had arguably catalysed deinstitutionalisation, and the research of Tizard & Grad (1961) and Kushlick (1965) provided some hope for a movement towards care in the community.

In fact, an 'elective', community-based approach had been developing for some time, with attempts being made particularly to distinguish between custodial institutions and acute treatment facilities. In the US, Dr Adolph Meyer suggested that psychiatry should look at the person in his environment and not at the disease. For the first time in 1905, social workers helped families rehabilitate ill relatives (Rosen, 1968). Aviram & Segal (1973) described how the community clinics derived their impetus from movements in child welfare and child guidance, and the growth of public awareness about mental health problems, as well as the influence of the mental hygiene movement. There was also official recognition of the large number of psychiatric patients from World War I for whom the organicists' efforts to diagnose and treat proved woefully inept (Showalter, 1987).

In the US, farm colonies were set up to relieve hospital overcrowding and during the depression of the 1930s, state hospitals initiated family care programmes, placing mentally ill patients in foster care (Segal & Aviram, 1978). In the UK, the 'therapeutic community' developed in military hospitals during World War II, as in the Northfield experiment (Bion, 1961). Psychoanalysis was a tool with an increasingly recognised potential (Jones, 1952), and other innovative psychological treatment methods were developed. The discovery of psychoactive drugs in France in the early 1950s further facilitated the movement away from the merely custodial function of psychiatry. However, although the community had been recognised for its own therapeutic potential, too often in practice discharge into the community meant a transfer from the frying pan into the fire (Jones, 1985; Sarteschi *et al*, 1985). In the UK, the community rehabilition of Graham Young from Broadmoor ended tragically (the uproar this caused in the House of Commons led, *inter alia*, to the Aarvold (Home Office & Department of Health and Social Security, 1973) and Butler (Department of Health and Social Security & Home Office, 1975) reports, drawing public attention to the particular rehabilitation difficulties facing forensic psychiatrists.

Current issues

A core group exists amongst the mental handicapped, the severely behaviourally disturbed, and the elderly, for whom community management remains particularly difficult; indeed, they act as a pawl against the ratchet movement of deinstitutionalisation. Yet at times, the 'forensic' ranks are swollen by patients perhaps not justifying segregation (Orr, 1978; Scannell, 1986). For example, difficult patients are often thrown upon community resources 'early', and it is easy to be prejudiced against them if facilities are already stretched. The small psychiatric units are reluctant to treat them, particularly if they have 'collected' a criminal charge, and it takes experience and forbearance to overcome this group's rejecting attitudes, when high professional achievement militates against a sympathetic approach (Bachrach, 1980; Martin, 1984).

Similarly, nursing these generally 'chronic' patients is as distressing and 'depleting' as nursing acutely ill (and dying) patients (Menzies, 1960). All this can lead to staff burn out. Thus these difficult and offender patients are often excluded from the mainstream of psychiatry. Torrey & Wolfe (1986) described the community mental health centres in the US as creaming off the 'worried well'. Probation services and social services do exemplary work, but they have become overburdened. The streets are filling not only with ex-psychiatric patients (US General Accounting Office, 1977), but also with untreated 'psychiatric patients' (Brickner *et al*, 1986). They are only the tip of the iceberg, and David (1988) hopes that the UK might avoid 'America's national tragedy', where homelessness is a way of life for many mentally disabled. Additionally, Scull (1984) has written of a 'New Custodialism', of patients overmedicated and institutionalised in their own homes, and Schmidt *et al* (1977) describe the morbidity simply being decanted from hospitals into nursing homes. The problem has become again a submerged one.

An additional factor from the American experience is the uneasy fit between legal restraints and psychiatric practice, and Stone (1985) asserts that the greatest iatrogenic problem of the mental health system today is the failure of continuity of care – 'legal reform has allowed us to rationalise our failures'. The requirement of unequivocal dangerousness with a recent act makes civil detention very difficult. Ill persons deteriorate and may eventually strike out or offend, and it is then that mental health laws can become operational, not before. Such legal restrictions and inadequacies in psychiatric care both contribute to the 'criminalisation' of the mentally ill. Teplin (1983) has reviewed the various ways a person's behaviour may be deemed disordered (justifying psychiatric intervention) or disorderly (warranting arrest).

The situation in the UK

The Glancy report (Department of Health and Social Security, 1974) examined the facilities for difficult patients in National Health Service hospitals, and identified a need for 1000 secure beds nationwide. The Butler report (Department of Health and Social Security & Home Office, 1975) identified the open-door policy as a major contributor to the inappropriate placement of offender patients in special hospitals and prisons. Two thousand beds on a national basis were recommended to be provided within so-called regional secure units (RSUs). The community care recommendations of the Butler report were, however, relatively unemphasised, compounding the stagnation of clinical care seen in special hospitals, as communities continued to be reluctant to rehabilitate these patients (*Lancet*, 1986); a similar fate threatens the population in the RSUs. Over ten years ago, Bowden (1977) expressed concern that the RSU development would ignore the needs of the large population of the remanded chronically disturbed recidivists. It was proposed (*Lancet*, 1986) that RSUs and special hospitals should be dismantled, and that this patient group should be managed within a flexible district-based service. This author recognises the importance of this thinking, but would not make so bold a proposal (Scannell, 1986). The liaison role familiar to forensic psychiatrists is akin to the community mental handicap teams utilising general as opposed to specialist health facilities (Bicknell, 1985), but there are self-evident problems, such as the RSUs silting up (*Lancet*, 1986) if the general psychiatric provision continues to suffer cutbacks. Butler's concept of an RSU as being only part of a comprehensive service for this client group has not been realised.

Discussion

A healthy controversy continues about the fate of the RSUs in the UK, and while Snowden (1987) wonders whether we should return to Scott's (1970) recommendation for treatment facilities within the prison service, others consider that district health authorities should take over the management of patients currently in special hospitals and RSUs (*Lancet*, 1986). There is at present a variety of regional forensic services, and clearly these different services should be properly evaluated before major policy changes are proposed.

An understanding of the vicissitudes of mental health resources is highly relevant for those planning the treatment of difficult and offender patients, as the size of this population may increase as the general psychiatric provision decreases. A continued emphasis on special-interest jobs may enable an *a priori* integration by further enhancing the liaison role. Bluglass's (1978) admonition that 'planning should concentrate on developing services . . . and move away from a pre-occupation with bricks and mortar' had, sadly, been poorly heard. Innovative treatment approaches and sophisticated community programmes enabled the initial movement away from institutions and, in their absence, the RSU development may initiate a period of reinstitutionalisation.

The Department of Health and Social Security hitherto has concentrated on funding the RSUs, leaving the development of supporting community services subject to the usual fiscal restraints (*Hansard*, 1984). However, the South West Thames Region, because it is building a much smaller unit, has recently obtained permission to allocate central RSU monies throughout the region at a district level, so minimising the gap between the unit and the district-based services.

Alternative housing and hostel provisions are crucial additional community resources (David, 1988). By not seeing the social needs early enough, we might well be seeing a reinstitutionalisation of the difficult and unrewarding patients, especially in the particularly deprived sectors of the community -the early signs of which are already showing, with an identified preponderance of West Indian patients in secure units and hospitals (Littlewood & Lipsedge, 1988; McGovern & Cope, 1987). Of equal concern, young black people are proportionally more likely to receive Section 53(2) sentences than other forms of (often more lenient) youth custody or detention centre disposals (NACRO, 1988). This litmus reading can be ignored only at great cost tó both patients and policy makers.

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The Glasgow Rehabilitation Survey

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To assess the future requirements for long-stay psychiatric beds, every consultant psychiatrist in Glasgow was asked to consider whether long-stay patients in his or her wards would be fit for rehabilitation and return to the community. For the purposes of the survey, long stay was defined as a single admission of at least six months, but patients with an organic diagnosis who were aged over 65 were excluded. It was estimated that, with rehabilitation, almost a third of the patients surveyed could return to the community, and that, with more participation in self-care, over 15% might be able to manage in a ward or hostel within the hospital. Patients judged fit to return to the community were preponderantly younger patients with a shorter period of in-patient care, and those suffering from a functional psychotic illness.

In Scotland, psychiatric facilities have continued to be dependent on the mental hospital and there is gross under-provision for alternative care in the community (SHHD, 1985). This is due in part to a more conservative view of psychiatric management, but an additional factor is doubtless the failure of community care programmes elsewhere to provide acceptable care for those with chronic incapacitating mental illness (House of Commons, 1985; Weller *et al*, 1986).

Greater Glasgow Health Board (GGHB) has responsibility for the provision of health services for just under one million people in the Glasgow conurbation, and is the largest health authority in the UK. There is hope that additional funding and resources will be invested in mental health as the SHAPE (Scottish Health Authorities Priorities for the 1980s) (SHHD, 1980) recommendations are implemented. SHAPE is the report of a working party set up by the Scottish Health Service Planning Council. The report suggests the need for a more equitable distribution of funds between specialities offering an acute service and those specialities which, in addition, accept a responsibility for continuing care. It further proposes in psychiatry that more facilities should be developed in the community and it emphasises the importance of rehabilitation and resettlement, envisaging co-operation between the National Health Service (NHS), local authorities, and the voluntary organisations – 'joint planning'. The size of the population served by Greater Glasgow Health Board has permitted the establishment of a separate mental health unit, and has provided a unique opportunity to examine the policy for managing the most disabled psychiatric patients.

We report here on a survey, carried out in October 1986, to assess the rehabilitation potential of every psychiatric long-stay patient in the catchment population of GGHB. Data from a census of psychiatric in-patients carried out in April 1987 provided the denominator for some of the data from the rehabilitation survey. It is our intention to repeat the exercise in five years' time in order to assess progress in rehabilitation and the development of planned community-based psychiatric services.

Method

All consultant psychiatrists with responsibility for long-stay psychiatric in-patients in the City of Glasgow were identified and asked to complete a questionnaire (available from MGL) for every in-patient under their care. For the purposes of the inquiry a long-stay patient was any who had had at least six months of in-patient care during the present admission, irrespective of diagnosis or age. Although patients over 65 were included in the survey, those from this age-group who had an organic diagnosis were excluded. The questionnaire requested details regarding hospital, ward, sex, date of birth, date of admission, length of stay in hospital, and diagnosis (ICD-9). Consultants were then asked to evaluate whether individual patients were suitable subjects for discharge to the community, or for more self-care in an area within the hospital, or were unsuitable for further rehabilitation.

To encourage co-operation, the assessment scale was designed to be completed rapidly by those who had a reasonable knowledge of the patients' level of functioning. The consultants were asked to make an estimate of an individual patient's potential to cope in the community, or in a ward or facility where they would be more independent. Consultation with other disciplines involved with the patient's care was recommended, but it was emphasised that completion of the survey was the remit of the responsible medical officer. This was done because discharge from hospital remains essentially an area of medical responsibility and because junior medical staff, frequently on rotation, may have only a limited experience of the ward. The survey was concerned with the patient's potential within two years and assumed adequate rehabilitation resources within the hospital and support services in the community.

Results

The census indicated that 3122 beds were occupied by patients with mental illness, including the elderly, in April 1987. This is equivalent to 3.2 beds per 1000 of the catchment population served. Although the denominator used is not, in fact, the population at risk for mental illness, since all those under the age of 18 are included, a previous survey carried out by one of us (Bryson, 1987) enables some comment to be made on the demography of the four Glasgow catchment areas. There is a significant excess of single, widowed and divorced males in the age groups 45 and over in the catchment area served by hospital B (see Table I), with a corresponding deficit in the population served by hospital C. In Glasgow as a whole compared with the remainder of Scotland, there is a significant deficit of married, and an excess of single, widowed and divorced adults (aged 16–64 for males, and 16–59 for females). Excluding the elderly with organic diagnoses, 1313 (1.3 per 1000 of the catchment population) of the beds were occupied by long-stay patients, a rate below that for the whole of Scotland in 1979 (1.6 per 1000) but greater than that projected for 1991 (1.2 per 1000) (SHHD, 1985).

Comparison with the rest of Scotland is further complicated by the fact that over 4 million of Scotland's 5.5. million population live in the highly urbanised central belt. One would, therefore, expect rates for admission to be higher for Glasgow than for the rest of Scotland because of the drift of people with serious mental illness towards urban centres. There has been, in addition, a reduction in the occupancy of long-stay psychiatric beds for the populations studied since 1979.

In the rehabilitation survey 1102 questionnaires were returned, representing 84% of the population under consideration. Completed survey forms were obtained relating to 597 males and 502 females, with 3 patients for whom sexual status was not recorded. The majority of those forms which were not returned related to patients over the age of 65, suggesting that a few consultants felt that all patients over 65 were to be excluded.

From the numbers of patients who were surveyed in each hospital, together with the catchment population of each hospital, a residence rate per 1000 of each hospital's catchment population was calculated (Table I). (The catchment areas given for hospitals only became fixed in 1974.) All four hospitals have an almost entirely urban catchment area. The rate of residence in long-stay care in each of the hospitals showed a wide range from 0.77 to 1.64 per 1000, suggesting that uniform criteria for admission and/or discharge from long-term care are not being applied throughout the city. Hospital A had the highest rate of residence. Rates of residence in all other hospitals were compared with it in turn. There was a statistically significant difference in the rates of residence in hospitals B, C and D ($\chi^2 = 16.52$, 68.38, 53.23 respectively; all $P < 0.001$) when compared with hospital A.

Table II shows a summary of the patients' assessed rehabilitation potential in each of the four hospitals. Hospitals estimated that, on average, 33% of patients could return to the community (95% confidence

TABLE I

Rate of residence in long-stay care per 1000 of the catchment population in the four Glasgow psychiatric hospitals

Hospital	*Current catchment population*	*Rate of residence in long-stay care per 1000 of the catchment population*
A	248 000	1.64
B	191 000	1.16
C	208 000	0.77
D	328 000	0.95

TABLE II

Assessment of rehabilitation potential

Hospital	*Patients assessed*	*Rehabilitation potential*			
		Community	*Lower dependency area in hospital*	*No rehabilitation possible*	*Not stated*
A	407	126 (31%)	24 (6%)	256 (63%)	1
B	223	69 (31%)	21 (9%)	132 (54%)	1
C	160	60 (38%)	43 (27%)	57 (36%)	0
D	312	101 (32%)	87 (28%)	122 (39%)	2
Total	1102	356 (32%)	175 (16%)	567 (52%)	4

interval = 29.5%–35.0%), representing 387–460 patients throughout Glasgow. When the proportion of patients in each hospital was compared with respect to capacity for return to the community, no significant difference was found ($\chi^2 = 2.50$, d.f. = 3, NS). The proportion of patients thought to be able to manage additional self-care, corresponding to 180–236 of Glasgow's long-stay psychiatric in-patients, was 16% (95% c.i. = 13.7%–18.0%).

Similarly, when the proportion of males and females in each of the three rehabilitation categories was compared, no significant difference was found ($\chi^2 = 1.9$, d.f. = 2, NS). These data are illustrated in Table III.

Consultants were then asked to judge which would be the most appropriate community setting for those patients whom they considered fit for rehabilitation and discharge to the community. Of 356 patients, 175 were thought to require the support of a warden in a sheltered housing complex or a community hostel placement, a group residence staffed by non-professional personnel. This compares with 110 patients said to require some form of group tenancy, either a group home (2–4 tenants), or a cluster flat (individual rooms with simple toilet and kitchen facilities and warden support), and 59 whom psychiatrists felt could cope in normal community accommodation, usually a flat provided by the local authority. For the remaining 15 patients assessed suitable for return to the community, the level of independent living was not specified.

TABLE III

Rehabilitation potential and sex, diagnostic category, age and length of stay of patients

Rehabilitation potential	*Male*	*Female*	*Not available*	*Total*
Community rehabilitation	193 (54%)	161 (45%)	2	356
Lower dependency area rehabilitation	86 (49%)	83 (49%)	3	172
No rehabilitation	314 (55%)	253 (45%)	0	567
Totals	—	—	—	—

Rehabilitation category	*Diagnostic category*						
	Functional psychosis	*Organic psychosis*	*Personality disorder*	*Neurosis*	*Other*	*Not Stated*	*Total*
Community rehabilitation possible	269	21	26	15	21	4	356
Lower dependency area rehabilitation possible	133	17	5	7	10	3	175
No rehabilitation possible	429	87	12	7	30	2	567
Total	831	125	43	29	61	9	1098

Rehabilitation potential	*Age (years)*		
	<45	*45–64*	*65+*
Community	74 (56%)	185 (34%)	90 (22%)
Low dependency ward in hospital	26 (20%)	88 (16%)	60 (15%)
No rehabilitation possible	32 (24%)	276 (50%)	258 (63%)
Total	132	549	408

Rehabilitation	*Length of stay*	
	6 months–5 years	*5 years+*
Community	130 (48%)	226 (28%)
Low dependency ward in hospital	34 (12%)	141 (17%)
No rehabilitation possible	110 (40%)	457 (55%)
Total	275	824

The proportion of males and females considered by consultants to be suitable for various community placements was next examined, using the χ^2 test. The proportion of males and females considered suitable for cluster flats, group homes, sheltered housing, ordinary or mainstream housing, and supported lodgings was similar. However, significantly more males were thought to require hostel care in the community ($\chi^2=4.8$, d.f. $=1$, $P<0.05$), and halfway housing ($\chi^2=8.4$, d.f. $=1$, $P<0.01$). These results indicate a male population more incapacitated, at least in social terms.

The diagnosis of patients judged to have potential for return to the community was considered (see Table III). When elderly patients with dementia were excluded, the overwhelming preponderance of patients remaining suffered from the functional psychoses. The proportion of patients with such a diagnosis in the three categories (community, lower dependency, no rehabilitation possible) was essentially the same, at 76%.

New long-stay patients in Glasgow are being recruited from those with functional illness. Of those patients in hospital for 6 to 12 months (the new long-stay patients), 64% had such a diagnosis, and 80% of those who had been in hospital for 12 months to 5 years also suffered from one of the functional psychoses.

The data collected from those patients whom consultants considered likely to be more able to cope with a hospital environment which makes more demands on them, showed a similar pattern. Of 175 patients 133 (76%) had a functional psychosis, and the largest remaining group had an organic psychosis.

To examine whether age was associated with rehabilitation potential, the proportion of patients in different age groups was compared with respect to the category assigned them by the assessing doctor (community, lower dependency ward, no change). Significantly more patients in the under-45 age group were considered to have potential to return to the community ($\chi^2=38.53$, d.f. $=4$, $P<0.001$) (Table III). Of those aged under 45, 76% were judged able to improve their level of functioning; of those aged 45–64, 50%; and of those aged 65 and over, 37%.

The association between length of stay and rehabilitation potential was next examined (see Table III). Only 28% of those patients who had been hospitalised for longer than 5 years were judged able to return to the community, as against 47% of those hospitalised for 6 months to 5 years ($\chi^2=36.70$, d.f. $=1$, $P<0.001$), but more patients in the longer stay category were thought able to benefit from a lower dependency area in the hospital.

Length of stay in hospital and age are linked. Obviously, younger patients will be less likely to have accumulated as lengthy a period of in-patient stay as older patients. Therefore, the rehabilitation potential of patients aged under 45 was analysed. Of 74 patients, 47 (60%) from this age group who had been in hospital for less than 5 years were thought to be fit for rehabilitation, compared with 13 of 58 (22%) in this age group who had been in hospital for longer than 5 years ($\chi^2=20.52$, d.f. $=1$, $P<0.001$). Thus a shorter length of stay is associated with greater rehabilitation potential, even when the effect of age is discounted.

Discussion

We believe this to be the largest complete survey of the rehabilitation potential of psychiatric in-patients in a discrete geographical area. In the opinion of consultants, almost a third of the patients surveyed would be able to live in the community if the appropriate facilities were present. This figure is very close to McCreadie *et al*'s (1985) estimate of 37% of new (Scottish) chronic in-patients judged able to cope with life in the community. Each hospital produced remarkably similar results here, providing a measure of face validity for the method used. Reliability studies might have improved the quality of data collection but, in view of the scale of the exercise, it would have been difficult to arrange and might have reduced the numbers of consultants prepared to participate in the study.

The data suggest that approximately 400 patients throughout Glasgow might return to the community. Almost 50% were thought to require either sheltered housing or hostels, and a further 30% a group tenancy or cluster flat. Facilities of this nature in Glasgow are wholly insufficient to meet this need, and community care for discharged long-stay psychiatric patients is usually placement in local authority housing with support by hospital staff. It would be interesting to know why consultants envisaged that on-site supervision would be important for such a large proportion of the discharged patient population.

In the present survey, hospitals fell into two groups regarding their view on whether patients could undertake more of their own self-care in hospital: two hospitals judged that less than 10% of patients were in this category and two that the figure was less than 30%. The discrepancy may relate more to the perception of individual consultants about whether this is a desirable approach to psychiatric management than to real inter-hospital differences between the patients. However, Wykes (1983), and more recently Goldberg *et al* (1985), have demonstrated that a very disabled group of chronic psychiatric in-patients is able to benefit from hostel-type accommodation in or adjacent to the hospital, and staffed by nurses. In addition, some of this group of people may be able to live outwith hospital if an appropriate community can be created for them (Wing & Furlong, 1986), i.e. a less stigmatising form of asylum.

McCreadie *et al* (1985) found that younger patients with a shorter duration of in-patient treatment were more likely to return to the community following admission to long-term psychiatric care. There were similar findings in the present survey. Another finding of McCreadie's group (McCreadie *et al*, 1983) was that the patients most likely to remain in the long-term wards of Scottish psychiatric hospitals were schizophrenic, although organic mental disorders (in the under-65s) formed a higher proportion of first admissions to long-term care. In the present survey a diagnosis of this group of functional psychosis (the vast majority of patients are likely to be schizophrenic) was, in addition to age and length of stay, associated with potential for rehabilitation.

An interesting feature of the present survey was the differing rates of residence for patients in long-stay care in each of the hospitals. While there are demographic differences in the catchment populations served by each of the hospitals, they all offer a service for a mainly urban population, namely a large sector of the City of Glasgow. Although the catchment population statistics can only be related with some certainty to the period from 1974 onwards, the data suggest differing criteria for admission or discharge throughout the city. It is tempting to think that the availability of beds is one of the main factors in determining admission to long-stay care. This, in turn, is likely to reflect the availability of community support and accommodation services, together with the availability of hospital-based services.

The number of patients judged unsuitable for rehabilitation was 567. This would be an interesting population to examine in more detail. The main association with poor rehabilitation prospects is length of stay as an in-patient. It is possible that a more gradual and graded approach towards rehabilitation might enable a proportion of these patients to function adequately in the community with support.

The results in this survey of long-stay psychiatric in-patients in Glasgow, relating to a catchment population of almost 1 million people, are, therefore, similar to those of previous work in Scotland (McCreadie *et al*, 1985) involving newly admitted long-stay in-patients. Glasgow, and Scotland, have been slow to implement programmes of community care as set out in the SHAPE report (SHHD, 1980) and *Mental Health in Focus* (SHHD, 1985). This survey shows that over 400 patients in Glasgow could be living in the community, provided that the Health Board and the local authority make adequate provision for community facilities.

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Community Management of Schizophrenia

A Two-Year Follow-Up of a Behavioural Intervention with Families

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The relapse and readmission rates of schizophrenic patients who participated in a controlled trial of a nine-month behavioural family intervention trial based on the EE status of their relatives are presented at two years. The patients who received the behavioural family intervention had lower rates of relapse and readmission than patients from high-EE homes who had received a short educational programme or routine treatment. The relapse rate of the behavioural family intervention group (33%) was the same as that of the low-EE group (33%), and significantly lower than that of the non-intervention high-EE group (59%).

Four controlled studies have reported the efficacy of psychosocial family intervention in reducing schizophrenic relapse in high-risk families (Leff *et al*, 1982; Falloon *et al*, 1982; Hogarty *et al*, 1986; Tarrier *et al*, 1988). Over 9–12 months, family interventions have reduced relapse rates to 0–19%, compared with 41–53% in control groups. Hogarty *et al* (1986) reported no relapses over 12 months in a group who received both family psychoeducation and management, and intensive social skills training for the patient, compared with 19%, 20%, and 41% relapse rates in patients who received family psychoeducation alone, social skills training alone, and a control group, respectively.

These groups of workers have also specified two-year follow-up relapse rates. Leff *et al* (1985) reported a 20% relapse rate in drug-complaint patients who received family intervention, compared with 78% in the control group, although if suicides and medication non-compliers are included, these figures rise to 50% and 83% respectively. Falloon *et al* (1985) reported a 17% relapse rate in the group who received family intervention compared with 83% in the control group. Hogarty *et al* (1987) reported two-year relapse rates of 25% (family intervention combined with social skills training), 32% (family intervention alone), 42% (social skills training alone), and 66% (control group).

All of these studies identified returning to live with a relative rated as high on expressed emotion (EE) as a high-risk factor for relapse (see also Leff & Vaughn, 1985; Koenigsberg & Handley, 1986).

In a previous paper we reported the relapse rates of our intervention at nine months (Tarrier *et al*, 1988). Patients with a high-EE relative were allocated to one of four groups, with the following nine-month relapse rates: behavioural intervention (enactive), 17%; behavioural intervention (symbolic), 8%; education, 43%; and routine treatment, 53%. Patients with low-EE relatives were allocated to two groups with the following rates: education, 22%; routine treatment, 20%. This paper reports the two-year relapse rates.

Method

Patients

Details of the patients and their relatives were given in the original report (Tarrier *et al*, 1988). Of the 73 patients who participated, one died of natural causes before the two-year follow-up point, and has been excluded from the analysis. Patients are included in the analysis as long as they commenced the intervention, as it was reasoned that if treatment dropouts were excluded from the analysis, the sample could be biased towards a good-outcome group, which would have less relevance for service provision.

During the two years, all patients were managed by their clinical team. Patients were maintained on neuroleptic medication; however, it was not feasible to do detailed monitoring of medication dosage and compliance, as it had been during the first nine months after discharge. The clinical teams endeavoured to maximise compliance, and there was no evidence of extensive or systematic drug non-compliance.

Assessment of relapse

In the initial study, assessment of relapse was carried out blind, by the use of the PSE/CATEGO. Unfortunately, as resources were not available to repeat the PSE at two-year follow-up, relapse was assessed by examination of patient admission records and case notes. This was felt to be justified, as all patients were in contact with the psychiatric services, and a major relapse would have a high probability of detection. If a patient who was well for the first nine months of the study was admitted 9–24 months after discharge from the index admission, then the hospital notes were examined. If the notes indicated that the patient had been admitted because of a recurrence or exacerbation of psychotic symptoms, then this was classified as a relapse. Examination of the records and notes was carried out by volunteers who were blind to the patients' treatment groups. Identified relapses were verified by the first author and confirmed in all cases.

In-patient admissions

The number of in-patient admissions, for any reason, of all patients over the two years was calculated for each treatment group.

Treatment groups

The original study had included six treatment groups, but relapse rates calculated at nine months suggested that these six groups could be reduced to three, owing to a lack of difference in relapse rates between the pairs of groups. Hence the Enactive and Symbolic groups were combined to form one behavioural intervention group; the high-EE education and routine treatment groups were combined to form a high-EE control group; and the two low-EE groups were combined to form one low-EE group. Details of the treatment groups and interventions are given elsewhere (Barrowclough *et al*, 1987; Barrowclough & Tarrier 1987*a*, 1987*b*; Tarrier *et al*, 1988). All families in the behavioural intervention group were offered the continued family intervention after the end of the formal nine-month intervention, through either telephone contact or formal sessions. Of these 24 families, four families requested at least one session, but only one family was seen regularly (once every six months). No families in the control groups received such specialist intervention.

Results

The relapse and admission rates are presented in Tables I and II respectively.

χ^2 analyses (one-tailed) were performed on both sets of data, with the following results: relapse rates, $\chi^2=4.46$, $P<0.05$; admission rates, $\chi^2=11.18$, $P<0.0001$; comparison between the relapse rates of the high-EE intervention and control groups, $\chi^2=3.37$, $P<0.05$. One-tailed analyses are justified because the treatment effect at two years is the same direction as the significant effect at nine months.

TABLE I
Relapse rates at two-year follow-up

	Relapses	
Behavioural intervention group (high-EE)	8/24	(33%)
Control group (high-EE)	17/29	(59%)
Low-EE group	6/18	(33%)

TABLE II
In-patient admissions over two years

	No. of admissions	*Ratio (admissions: patients)*
Behavioural intervention group (high-EE)	17	0.71:1
Control group (high-EE)	27	0.93:1
Low-EE group	9	0.5:1

Discussion

It must be acknowledged that readmission rates are a weak representation of relapse rates, and this must temper our conclusions, although blind assessments should restrain any systematic bias.

Our results are close to those of the other English study (Leff *et al*, 1985), in which there was a 33% difference between the relapse rates of the intervention and control group at two years when suicides and medication non-compliers are included. This can be compared to the North American studies of Falloon *et al* (1985), in which there was a 66% difference between the intervention and control groups, and Hogarty *et al* (1987), who reported a 34% difference between family intervention and the control group, and a 41% difference between combined family intervention and social skills training and the control group.

Patients in our control group appeared to do rather better between 9 and 24 months than those in two other studies, with 59% relapses in two years compared with 83% found by both Falloon *et al* (1985) and Leff *et al* (1985), but were approximately equivalent to the 66% reported by Hogarty *et al* (1987). The relapse rate of our high-EE control group at nine months was 48%, and the increase to 59% at two years was due to the relapse of only a further three patients during the subsequent 15 months.

It is apparent that the short education programme does not significantly reduce relapse rates. Within the high-EE control group, the education-only group had 8/14 (57%) relapses compared with 9/15 (60%) in the routine treatment group. Two of the three relapses in the high-EE control group between 9 and 24 months were in the education-only group. This failure of an education programme to prevent relapse needs to be emphasised so as to discourage the implementation of education programmes in isolation as an alternative to long-term family management as a clinical service. These results suggest that the behavioural family intervention may have merely delayed relapse as opposed to preventing it, since the proportion of relapses in the intervention group increased after the first nine months. Five of the eight (63%) relapses in the intervention group occurred after the first nine months, compared with 18% in the control group. Other studies of family intervention (Leff *et al*, 1985; Hogarty *et al*, 1987), social skills programmes (Wallace & Liberman, 1985), and out-patient family crisis therapy (Langsley *et al*, 1971) have also indicated this delay of relapse.

A variant of this explanation is that relapse risk was reduced only while the intervention was being implemented. Once the behavioural intervention was terminated, the risk of relapse was again increased. Test & Stern (1978), in a review of mainly North American studies on the community treatment of chronic psychiatric patients, concluded that positive results were maintained only as long as special community treatment programmes were in effect.

Unfortunately it was not possible to reassess EE at two years, and all patients were analysed on the basis of their original group allocation. There is evidence that some high-EE relatives will change to low-EE over time (e.g. Brown *et al*, 1972), which may reduce their relative risk; in this study, in the initial nine months, 38% of high-EE relatives in the education and routine treatment groups did in fact change from high-EE to low-EE (Tarrier *et al*, 1988). If changes from high-EE to low-EE explain the lower relapse in the intervention group, a similar change would be expected in the high-EE control group. Relapse rates between these two groups, however, are significantly different.

The most probable explanation for these results is that in some vulnerable patients, the family intervention delayed relapse, but without continued intervention the risk of relapse is high. Psychophysiological data (Tarrier & Barrowclough, 1987; Tarrier, 1989) suggest that even in families in which relatives have changed from high to low EE, the arousal levels and reactivity of the patient remain high. This could indicate a continued high risk of relapse, which could last for some months after the relatives have changed EE status. The effect of life events on arousal levels and relapse could also be influential. Although the occurrence of life events between 9 and 24 months is unknown, during the first nine months the behavioural intervention group experienced significantly more independent life events than the other two groups (Tarrier & Barrowclough, 1989). Since these life events were independent of the patients' behaviour, this result is difficult to explain, but the intervention may have resulted in the patients becoming more active, and hence more likely to experience life events, even if their behaviour had not directly caused the event.

There is also evidence that life events increase the arousal reactivity towards the relative (Tarrier *et al*, 1979). It is interesting to speculate that the proliferation of relapses in the behavioural intervention group after nine months could have been mediated through elevated arousal levels, caused in part by the high frequency of life events. The relationship between interventions, frequency of life events, and arousal levels needs further investigation.

Patients in the high-EE control group had a greater readmission rate compared with the intervention group and low-EE group, although it is probable that the low number of relapses in the latter two groups contributes greatly to this result. However, of the 17 admissions from the intervention groups, five were for one patient; this patient and her husband had dropped out of treatment at an early stage of the intervention and she had repeatedly relapsed over the subsequent months.

The nine-month and two-year results of this family intervention study strongly argue for routine family intervention in the community management of schizophrenia. This is supported by the results of similar studies (Leff *et al*, 1982, 1985; Falloon *et al*, 1982, 1985; Hogarty *et al*, 1986, 1987). The two-year follow-up results presented in this paper suggest that to prevent a proliferation of relapses after nine months, intervention should not be time limited, and many patients and their relatives may need continued intervention or 'booster' sessions, as recommended by Wallace & Liberman (1985). This will have implications for staff training and resource allocation. There are also strong suggestions, both from this project and from a DHSS-sponsored project also carried out in Salford Health Authority on the co-ordination of after-care for people with schizophrenia (Whitehead, 1987), that new methods of team work and case management need to be implemented for the effective community care of people with schizophrenia.

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PRESCRIBING INFORMATION
Presentation: Prothiaden is Dothiepin Hydrochloride B.P. an antidepressant of the tricyclic group. It is available as 25mg capsules and 75mg tablets. **Uses:** Prothiaden is indicated in the treatment of depression and associated anxiety. **Dosage:** Prothiaden should be given in a dosage of 75 to 150mg daily, based on response and severity. This may be taken as a single evening dose. In certain circumstances, i.e. in hospital use, Prothiaden has been given in dosages up to 225mg daily. Elderly – half the normal dose may be sufficient. **Precautions and Contra-indications:** Prothiaden has anticholinergic properties, therefore, it may precipitate urinary retention in susceptible individuals and its use should be avoided in patients with existing or potential urinary retention. Prothiaden should not be used in patients with closed-angle glaucoma. Caution is advised when treating epileptic patients and those with cardiovascular disorders. Prothiaden should not be used with MAO inhibitors nor within 14 days of ceasing such treatment. It may modify the action of some CNS depressants, catecholamines and hypotensive agents. **Side Effects:** These are usually mild and normally controlled by reducing the dosage. The following have been reported: dryness of mouth, constipation, disturbed accommodation orthostatic hypotension, palpitations, somnolence, tremor, headache. **Basic N.H.S. Price:** 28 × 75mg £4.00 as at 1st Oct. 1987. **Product Licence Numbers:** PL0014/5941, PL0014/0209. ® The Boots Company PLC., Nottingham, England. Further information available on request. References: 1. Data on file, March 1987. ETH 1174-9/87

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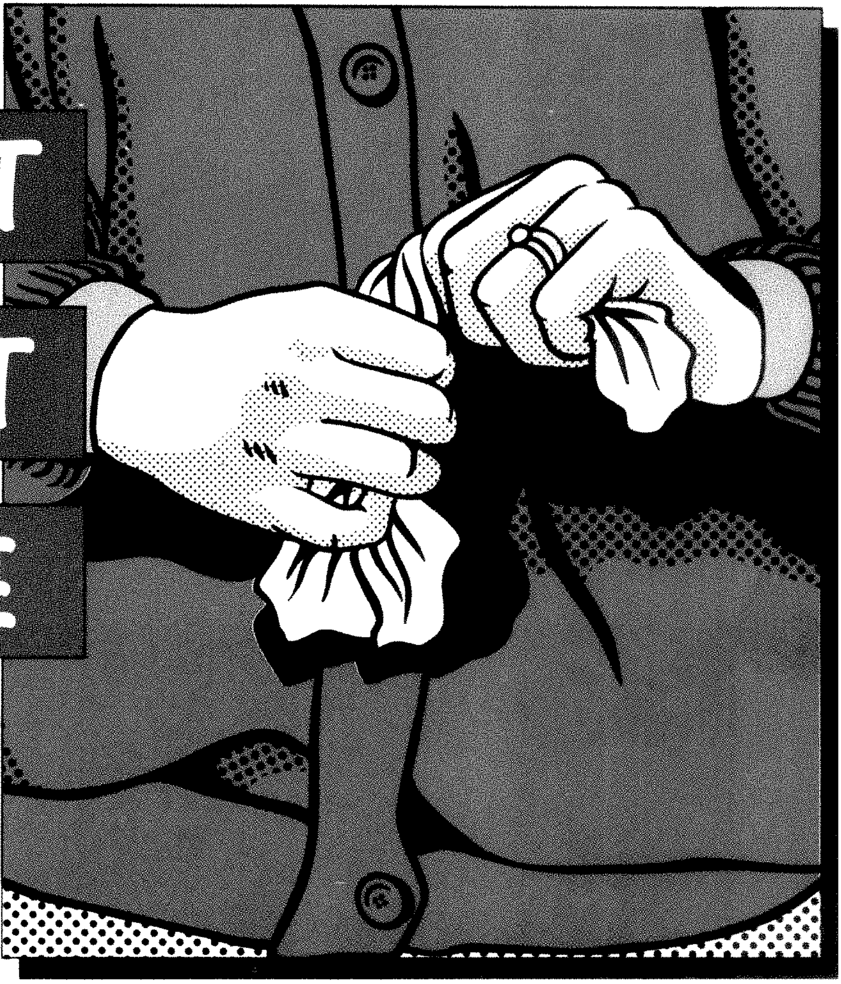

A common cry for help. Perhaps triggered by one or ore factors. But, all too often, iagnosis of the root cause of their problem is clouded by nxiety or somatic symptoms masking the underlying condition. You can trust rothiaden to brighten up their lives.

After 18 years of clinical experience, Prothiaden's tolerability is known, its erformance in clinical trials unsurpassed, which is why Prothiaden is prescribed by more GP's than any other antidepressant.[1]

o, paint a brighter picture for ur elderly patients who find they can't cope – with a prescription for Prothiaden.

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Prozac is a new antidepressant with efficacy equal to the standard tricyclics.[1,2] As a specific inhibitor of presynaptic reuptake of serotonin it has virtually no effect on the reuptake of histamine, acetylcholine or noradrenaline.[3]

Therefore efficacy is achieved without the usual accompanying sedation,[4] so patients' psychomotor performance normally maintained.[4-6]

Anticholinergic side-effects are l
frequent and severe than those of tricy
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It is also reassuring to know that
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Abbreviated Prescribing Information ▼

Prozac (fluoxetine hydrochloride)

Presentation Capsules containing 20mg fluoxetine hydrochloride

Uses Treatment of the symptoms of depressive illness

Dosage and Administration (For full information, see data sheet) Prozac is administered u

Adults A dose of 20mg/day is recommended. The maximum daily dose should not exceed

Because of the long elimination half-lives of the parent drug and its major metabolite, cha in dose will not be fully reflected in plasma for several weeks

The elderly The maximum total daily dose should not exceed 60mg

Children Not recommended

Patients with renal and/or hepatic dysfunction See 'Contra-indications' and 'Precautions' se

Contra-Indications

Hypersensitivity to fluoxetine. Prozac should not be administered to patients with severe failure (GFR < 10 ml/min)

Usage in nursing mothers Prozac should not be prescribed to nursing mothers

Warnings

Monoamine oxidase inhibitors At least 14 days should elapse between discontinuation of an and initiation of treatment with Prozac. At least five weeks should elapse between disconti of Prozac and initiation of therapy with an MAOI

Rash Prozac should be discontinued upon appearance of rash

Usage in pregnancy The safety of Prozac in human pregnancy has not been established

Precautions

Prozac should be avoided in patients with unstable epilepsy and it should be discontinued patient who develops seizures

A lower dose of Prozac, eg alternate day dosing, is recommended in patients with sign hepatic dysfunction or mild to moderate renal failure (GFR 10-50ml/min)

Caution is advisable when Prozac is used in patients with acute cardiac disease

Prozac may cause weight loss

There is little clinical evidence of the concurrent administration of fluoxetine with E lithium therapy

Drug interactions Increases of previously stable plasma levels of other antidepressants hav observed when Prozac has been administered in combination

Agitation, restlessness and gastrointestinal distress have been reported in five pa receiving fluoxetine in combination with tryptophan

Pharmacokinetic data suggest that the half-life of diazepam may be prolonged in some pa

For further information, see data sheet

Side-effects

The following treatment-emergent adverse events were observed during placebo cont clinical trials at a frequency of one per cent or greater and at a significantly higher incidenc placebo (P value ≤ 0.05)

Asthenia, fever, nausea, diarrhoea, mouth dryness, appetite loss, dyspepsia, headache, nervousness, insomnia, drowsiness, anxiety, tremor, dizziness, fatigue, decreased libido, pharyngitis, dyspnoea, excessive sweating, (rash, see 'Warnings'), sexual dysfunction

The more common events listed above that caused discontinuation include nausea, he nervousness, insomnia, anxiety, dizziness and asthenia

Other events that have been reported include vomiting and convulsions

During pre-marketing testing hypomania or mania occurred in approximately 1 per fluoxetine treated patients

Elevated serum transaminase values and/or depressed leucocyte counts without accomp symptoms occurred infrequently in patients given fluoxetine

Hyponatraemia (including serum sodium below 110mmol/l) has been rarely reported

Overdose As of December 1987, there have been two deaths in patients who took overd fluoxetine in combination with other drugs (maprotiline, codeine, temazepam). Except fo deaths, all other 36 overdose cases which involved fluoxetine either alone or in combinatio other drugs and/or alcohol recovered without complications

One patient who reportedly took 3000mg of fluoxetine experienced 2 grand mal seizur remitted spontaneously

Legal Category POM **Product Licence Number** 0006/0195

Basic NHS Cost £27.44 per pack of 28 capsules **Date Of Preparation** Novemb

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8. Data on file, Dista Products Limited

Full Prescribing Information is available from: Dista Products Limited, Dextra Court, Chapel Hill, Basingstoke, Hampshire RG21 2SY. Telephone: Basingstoke (0256) 52011

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Just one 20mg capsule a day allows tients to resume and cope with eir normal everyday activities while their pression is controlled.

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Your depressed
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GAMANIL

lofepramine

viated **Prescribing Information.** ▼ GAMANIL. **Presentation:** Round, film coated, brownish violet tablets with spindle shaped scoring on one side, containing lofepramine hydrochloride equivale
ng lofepramine base. **Use:** Treatment of symptoms of depressive illness. **Dosage and Administration:** Adults: Usually 140 mg to 210 mg per day in divided doses. Higher doses may be given at
ion of the physician. Children: No dosage yet established. Elderly: Elderly patients may respond to lower doses in some cases. **Contra-indications:** Impaired hepatic function, mania, severe re
nent, heart block, cardiac arrhythmias, or during the recovery phase following a mild myocardial infarction. **Precautions and Warnings:** Use with caution in patients with cardiovascular disea
angle glaucoma, symptoms of prostatic hypertrophy, a history of epilepsy. Ability to drive a car and operate machinery may be affected. Therefore caution should be exercised initially until the indivi
n to treatment is known. **Side Effects:** Usually mild and transient, but include dryness of mouth, constipation, disturbed accommodation, tachycardia, hesitancy of micturition, dizziness, drows
nsion, sweating and tremor; rarely, allergic skin reactions, thrombocytopenia. Rises in liver enzymes have been observed as an incidental finding. There have been a few reports of jaundice. The
ns are reversible on cessation of therapy. Other characteristic tricyclic side effects can possibly occur. **Drug Interactions:** May occur with monoamine oxidase inhibitors, sympathomimetic ager
rgic neurone blocking drugs, alcohol, anaesthetics, barbiturates. **Use in pregnancy and breast feeding:** Not advised unless there are compelling medical reasons. **Overdosage:** Treatmen
matic and supportive. It should include gastric lavage and routine close monitoring of cardiac function. **Legal Category:** POM. **Package Quantities and Price to NHS:** Calendar packs of 4×
Packs of 250 tablets — Cost per day of 70 mg bd ex calendar pack 35.6p at 1.8.88. **Product Licence Number:** 70 mg tablets: PL 0493/0060, PA 54/23/2. E. Merck Ltd, Four Marks, Alt
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Family History and Cerebral Ventricular Enlargement in Schizophrenia
A Case Control Study

MICHAEL J. OWEN, SHÔN W. LEWIS and ROBIN M. MURRAY

Ventricular size was measured from CT scans in 48 patients meeting RDC for schizophrenia who had a first-degree relative with a history of treatment for major psychiatric disorder, in 48 age- and sex-matched schizophrenic patients with no such history in first- or second-degree relatives, and in 48 matched, healthy controls. There was no difference in ventricular size between those with and without a positive family history, although both groups showed ventricular enlargement with respect to normal controls. Ventricular enlargement was demonstrated in the subgroup of 23 patients with a family history of schizophrenia, but not in the subgroup of 18 patients with a family history of affective disorder. These observations provide further evidence that schizophrenics with a family history of affective disorder may constitute an aetiologically distinct subgroup.

The finding of cerebral ventricular enlargement in schizophrenia has been frequently replicated (Reveley, 1985; Owen & Lewis, 1986). That this reflects predominantly environmental, rather than genetic, factors was suggested by the observation that, in monozygotic twin pairs discordant for schizophrenia, ill twins have larger ventricles than both their cotwins and normal controls (Reveley *et al*, 1982). Moreover, in a subsequent study, ventricular enlargement was not seen in schizophrenic twins with a genetic predisposition that was manifested as major psychiatric illness in other members of the family (Reveley *et al*, 1984). Similar results have been obtained in studies of schizophrenic singletons (Reveley & Chitkara, 1985; Cazullo *et al*, 1985; Turner *et al*, 1986; Owen *et al*, 1987). The inverse correlation between manifest genetic predisposition and ventricular enlargement appeared to illuminate the nature of the relationship between genetic and environmental factors in the aetiology of schizophrenia: it implied that a causal continuum exists, with genetic factors at one pole and environmental at the other (Murray *et al*, 1985; Lewis *et al*, 1987), rather than most cases of schizophrenia resulting from a similar combination of genetic and environmental effects.

However, several studies have failed to find an inverse relationship between ventricular enlargement and family history (Campbell *et al*, 1979; Nasrallah *et al*, 1983; Pearlson *et al*, 1985; Owens *et al*, 1985; Farmer *et al*, 1987; Nimgaonkar *et al*, 1988). In some of these, the sample size was small (Campbell *et al*, 1979; Pearlson *et al*, 1985; Farmer *et al*, 1987). Even so, this is still a controversial issue, which the present study set out to clarify.

We examined computerised tomography (CT) scans from a large number of schizophrenic patients in order to reduce the likelihood of a type-II error. We also defined family history in several different ways, because some of the studies that demonstrated the inverse relationship included as having a positive family history those patients whose relatives had any major psychiatric disorder (Reveley *et al*, 1984; Reveley & Chitkara, 1985; Owen *et al*, 1987). In particular, a number of patients were included solely upon the basis of a family history of affective disorder. This strategy can be questioned. Firstly, although some claim that there is a genetic link between schizophrenia and affective disorder (Crow, 1986; Gershon *et al*, 1988), the majority view is that these disorders are genetically distinct (Gottesman & Shields, 1982; Baron *et al*, 1983; Kendler *et al*, 1985). Secondly, outcome in illnesses diagnosed as schizophrenic is better in patients with a family history of affective disorder (Pope & Lipinski, 1978; Kendler & Hays, 1983; Kendler & Tsuang, 1988), while ventricular enlargement tends to be associated with poor prognosis (Williams *et al*, 1985). Thus, the inclusion of patients with a family history of affective disorder, rather than only those with a family history of schizophrenia, may have contributed to the finding of smaller ventricles in those with a positive family history.

Method

Subjects

Subjects were drawn from the mixed population of psychiatric, neurological, and neurosurgical patients who had undergone CT scanning at the Maudsley Hospital between June 1977 and December 1983, inclusive. During this period, 21 500 scans were performed. Patients were assessed for inclusion if they (a) had been admitted to the Bethlem Royal or Maudsley hospitals, (b) had a most recent ICD-9 (World Health Organization, 1978) discharge diagnosis of schizophrenia, including schizoaffective disorders, (c) did not have a concurrent diagnosis of epilepsy, (d) were of singleton birth, and (e) were aged less than 65 years. These criteria were fulfilled by 255 patients. Case notes were then examined, and individuals excluded if there was a history of excessive alcohol use or dependence, or of intracranial surgery. Finally, those patients whose symptoms did not fulfil Research Diagnostic Criteria (RDC; Spitzer *et al*, 1981) for schizophrenia or schizoaffective disorder, schizophrenic type, were excluded, leaving 228 subjects.

The case notes of all eligible patients were further examined for evidence that a first-degree relative had been treated for major psychiatric illness. At the Bethlem and Maudsley hospitals, information concerning family history is obtained in a standardised fashion according to clearly defined guidelines (Hill, 1972), usually from interview with at least one relative as well as the patient. Major psychiatric illness was defined as schizophrenia, schizoaffective disorder, manic-depressive psychosis (as defined in ICD-9), or unspecified psychosis. Nine patients with a first-degree relative who had committed suicide, and for whom no diagnostic information was available, were excluded. Forty-eight patients (26 men, 22 women) had a positive family history, and these patients were further subdivided as follows:

(a) Family history of schizophrenia (FHSZ: $n=23$, 12 men, 11 women): a first-degree relative had a diagnosis of schizophrenia ($n=22$) or schizoaffective disorder ($n=1$) according to the Family History RDC (Endicott *et al*, 1975). For 13 of the relatives, including the one with a diagnosis of schizoaffective disorder, it was possible to obtain case records, and all of these supported the RDC for schizophrenia.
(b) Family history of affective disorder (FHAD: $n=18$, 14 men, 4 women): a first-degree relative satisfied the Family History RDC for major affective disorder. All these relatives fulfilled the criteria for depressive rather than manic disorder.
(c) Family history of unspecified functional psychosis (FHOTH: $n=12$, 7 men, 5 women): the available information did not allow Family History RDC diagnoses of affective disorder, schizoaffective disorder, or schizophrenia to be made in ill relatives. However, in all cases the Family History RDC for unspecified functional psychosis were satisfied.

Differences between the mean ages of the three groups were small (FHSZ 32.5 years, FHAD 31.8 years, FHOTH 32.2 years) and not statistically significant. Five patients with more than one affected relative were eligible for two groups (two for FHSZ and FHAD, two for FHAD and FHOTH, and one for FHSZ and FHOTH). One patient was eligible for all three groups. Exclusion of these subjects from analysis of the CT findings did not alter the pattern of results obtained, and these data are not reported. Two patients with a positive family history could not be assigned to one of the three subgroups.

In 123 of the remaining patients, family history was negative for major psychiatric illness or suicide in either first- or second-degree relatives. From this group, control subjects with a negative family history, of the same sex, and whose age at scan was the same to within three years, were selected for each of the subjects with a positive family history. The mean ages of those with and without a positive family history were 32.5 years and 32.2 years respectively.

Comparisons were also made with a healthy control group of 48 volunteers, each of whom was matched in the same way for sex and age with a subject with a positive family history. These volunteers were drawn randomly from a pool of control subjects who had been recruited either from hospital staff or members of the Salvation Army. None of the controls had a history of alcoholism, psychiatric illness, or major physical illness. The mean age of the normal control group was 34.3 years.

Thus, 48 age- and sex-matched triads of subjects were studied. The patients were selected independently of those we have studied previously (Owen *et al*, 1987, 1988). However, 27 of them were members of the previous series.

CT scanning

All CT scans had been performed on a 1010 head scanner. The size of the lateral ventricles and of the intracranial space in each of the 144 subjects was measured prospectively by mechanical planimetry from the cut showing the largest area of lateral ventricle. Each scan was measured independently by MJO and SWL blind to the status and identity of the subject. Inter-rater reliability was good ($r=0.98$). The ventricular: brain ratios (VBRs) were calculated from the mean values of both investigators, according to the method of Synek & Reuben (1976).

Affective symptoms

Affective symptoms in the patients were also assessed, blind to the CT findings and to the family history. Available case records from all episodes of the patients' illnesses that had resulted in admission to the Bethlem and Maudsley hospitals were examined to determine whether affective symptoms had ever been present to a degree sufficient to warrant an RDC diagnosis of either definite or probable major affective disorder or schizoaffective disorder.

Results

VBR

The mean VBRs for the various groups are shown in Table I. Statistical comparisons between groups were performed using the paired *t*-test. All 96 schizophrenic patients were compared with the 48 healthy controls by taking the mean of each matched pair of patients. VBR was significantly greater in the patients than in the controls ($t=2.67$, d.f. $=47$, $P<0.02$, two-tailed). VBR was also significantly

TABLE I
Mean VBR in each group of subjects

Group	n	*VBR*	*s.d.*
Schizophrenic patients[1]	96(95)	8.40(7.81)	7.21(4.25)
Negative family history	48(47)	9.14(7.95)	9.04(3.84)
Positive family history	48	7.66	4.61
FHSZ	23	8.37	5.81
FHAD	18	6.21	2.91
FHOTH	12	8.04	2.50
Healthy controls	48	6.22	2.34

1. One of the schizophrenic patients with a negative family history had a VBR of 65.36. Values with this subject excluded are given in parentheses.

greater in schizophrenic patients both with and without a positive family history when they were compared separately with the control group (negative family history v. controls, $t=2.12$, d.f. $=47$, $P<0.05$; positive family history v. controls, $t=2.30$, d.f. $=47$, $P<0.05$). Patients with a family history of schizophrenia had significantly larger VBRs than their matched healthy control group ($t=2.21$, d.f. $=22$, $P<0.05$), as did those with a family history of unspecified functional psychosis ($t=2.63$, d.f. $=11$, $P<0.05$). In contrast, there was no difference in VBR between patients with a family history of affective disorder and their matched healthy controls ($t=0.15$, d.f. $=17$).

The VBRs of the 48 patients with a positive family history did not differ significantly from those in the 48 patients with a negative family history ($t=1.08$, d.f. $=47$). Furthermore, the 23 FHSZ patients did not differ in VBR from their matched patient group with a negative family history ($t=0.89$, d.f. $=22$). Neither did the 12 FHOTH patients differ from their matched patients with a negative family history ($t=0.22$, d.f. $=11$). However, the 18 FHAD patients had significantly smaller VBRs than the matched patient group with a negative family history (means $=5.84$ v. 7.76, $t=2.17$, d.f. $=17$, $P<0.05$, two-tailed).

Ten patients had VBRs of greater than two standard deviations above the control mean. These were equally distributed between the two patient groups. Three had a family history of schizophrenia and none had a relative with affective disorder.

Affective symptoms

Statistical comparisons were performed using the unpaired t-test and Fisher's exact test. As can be seen from Table II, there was a trend for affective symptoms to be more common in patients with a positive family history than those without (44% v. 35%), but this was not statistically significant ($z=0.62$). This trend was largely because affective symptoms were particularly common in patients with a family history of affective disorder (67%). Indeed, affective symptoms were significantly more common in the FHAD patients than in patients with negative family history ($z=2.15$, $P<0.05$, two-tailed). The difference between the FHAD and the FHSZ groups achieved acceptable levels of statistical significance on a one-tailed test ($z=1.88$) (patients with a family history of both schizophrenia and affective disorder were excluded).

Among the schizophrenic sample as a whole, patients with affective symptoms did not have significantly smaller ventricles than those without (mean VBR $=7.55$ v. 8.96, $t=0.93$, d.f. $=94$). Indeed, when the one patient with extreme ventriculomegaly was excluded (see Table I), the means hardly differed (7.55 v. 7.89). Neither was a relationship between affective symptoms and ventricular size seen when the FHAD group was considered alone (mean VBR of patients with affective symptoms $=6.40$, mean VBR of those without $=5.84$, $t=0.37$, d.f. $=16$). However, among those patients with affective symptoms, there was a trend for those with a family history of affective disorder to have smaller VBRs than those patients with no family history (mean $=6.40$ v. 7.88, $t=1.38$, d.f. $=27$).

Discussion

The present case-control study confirms the well replicated finding of cerebral ventricular enlargement in schizophrenia (Reveley, 1985; Owen & Lewis, 1986). We have, however, failed to confirm the finding of an inverse relationship between family history and ventricular enlargement (Reveley *et al*, 1984; Reveley & Chitkara, 1985; Cazullo *et al*, 1985; Turner *et al*, 1986; Owen *et al*, 1987). No difference

TABLE II
Prevalence of affective symptoms in each group of subjects

Affective symptoms	*All patients (n = 96)*	*Negative family history (n = 48)*	*Positive family history (n = 48)*	*FHSZ (n = 23)*	*FHAD (n = 18)*	*FHOTH (n = 12)*
Probable	8	5	3	1	2	0
Definite	30	12	18	7	10	5
Total	38(40%)	17(35%)	21(44%)	8(35%)	12(67%)	5(42%)

The table shows the number of cases in each group in which evidence was found, in an episode of illness, of affective symptoms sufficient to fulfil the RDC for either definite or probable major affective disorder or schizoaffective disorder.

in ventricular size was observed between patients with and without a history of schizophrenia in a first-degree relative, both groups having larger ventricles than matched healthy controls. In contrast, patients with a family history of affective disorder did not show enlarged ventricles relative to those of healthy controls, and had significantly smaller VBRs than matched patients without a family history of major psychiatric illness.

This last finding suggests that the inclusion of patients with a family history of affective disorder as having a positive family history may well have contributed to the discrepancy between the results of three studies (Reveley *et al*, 1984; Reveley & Chitkara, 1985; Owen *et al*, 1987), and the present and other findings (Campbell *et al*, 1979; Owens *et al*, 1985; Farmer *et al*, 1987; Nimgaonkar *et al*, 1988). However, two of the studies that found a significant effect of family history on ventricular enlargement included only those patients with a family history of schizophrenia (Turner *et al*, 1986; Cazullo *et al*, 1985). It is of interest that Turner *et al* reported data from probands suffering their first episode of schizophrenia (mean age 24 years) and Cazullo *et al* also studied young patients (mean age 26 years), whereas those studies that have failed to find an inverse relationship between a family history of schizophrenia and ventricular size were all of older patients (Campbell *et al*, 1979; Owens *et al*, 1985; Farmer *et al*, 1987; Nimgaonkar *et al*, 1988). On the present evidence, therefore, we cannot exclude the possibility that the inverse relationship predicted by Murray *et al* (1985) is present in young patients near the onset of their illnesses, but is obscured over time by the effects on ventricular size of such non-specific factors as age, drug administration, alcohol abuse, and longitudinal sampling artefacts (Lewis *et al*, 1988).

Kendler & Hays (1983) found that schizophrenic patients with a family history of affective disorder were more likely to experience affective symptoms, and blind assessment of available case reports for our probands supported this. Moreover, affective symptoms did not predict *per se* the absence of ventriculomegaly either in the sample as a whole or when only the FHAD group was considered. Although depressive symptoms are more likely to supervene, outcome in schizophrenic patients with a family history of affective disorder is better both in the short- and long-term (Kendler & Tsuang, 1988). In a recent study, this effect was seen only in probands with a family history of unipolar depression and not when ill relatives suffered from bipolar disorder (Kendler & Tsuang, 1988). These findings seem pertinent to those of the present study, both because subjects in the FHAD group all had a family history of major depression and in view of reports that a positive relationship exists between ventricular enlargement and poor outcome in schizophrenia (Williams *et al*, 1985). Keshavan *et al* (1988) reported that schizophrenics with a family history of affective disorder were more likely than other schizophrenics to have abnormal dexamethasone and thyrotrophin-releasing hormone tests, and in these respects resemble patients with affective disorder.

The findings reviewed above raise the question of whether affective disorder is more common in the relatives of schizophrenic patients than in the general population. Two carefully executed, controlled family interview studies of schizophrenic probands with 'narrow', chronic forms of the illness as defined in DSM–III have failed to find an increased risk of affective disorder in relatives (Baron *et al*, 1983; Kendler *et al*, 1985). However, several other studies have reported a raised prevalence of affective illness in relatives (reviewed by Pope & Lipinski, 1978). A recent, large family interview study found a significant excess of unipolar, but not bipolar, affective disorder in the relatives of RDC schizophrenic probands as compared with healthy volunteers (Gershon *et al*, 1988).

If there is a relationship between family history of affective disorder and schizophrenia, how can it be explained? First, it may result from the misclassification of schizophrenic patients. Thus a number of patients with affective symptoms and in whom outcome is good may, in reality, have affective disorder. However, this could not adequately explain Kendler & Tsuang's (1988) data. It is also not easy to see how misclassification could account for the present findings, since ventricular enlargement is seen in some cases of affective disorder (Pearlson & Veroff, 1981; Nasrallah *et al*, 1982; Targum *et al*, 1983; Rieder *et al*, 1983; Pearlson *et al*, 1985; Dolan *et al*, 1985) as well as in schizophrenia.

A second possible explanation is that genetic liability to affective disorder simply exerts a pathoplastic effect on schizophrenia. This could readily account for the data on affective symptoms, and possibly also those on outcome. However, it is hard to see how it could explain an increased risk for affective disorder in the relatives of schizophrenic probands. One would also have to postulate that genetic liability to affective disorder somehow protects against ventricular enlargement.

A third possibility is that cases of schizophrenia with a family history of affective disorder result from the presence of genetic liability to both disorders, and from the ability of the resulting phenotypes to interact to produce illness without the need for environmentally produced brain damage. Such subjects would be expected to have more frequent affective symptoms, relatively good outcome and not to show ventricular enlargement on CT scan. Interaction between the phenotypes might take place at subclinical, as well as clinical, levels of expression. For example, a genetic liability to affective disorder might render an individual with genetic liability to schizophrenia more likely to develop a psychotic illness in response to stressful life events (Owen & Nimgaonkar, 1987).

The results of the present study should be interpreted in the light of several methodological limitations. Firstly, the patients all underwent CT scanning for clinical rather than research reasons. The proportion of patients scanned at the Maudsley Hospital is high compared with other psychiatric hospitals (Owen *et al*, 1988), reflecting the ready availability of neuroradiological facilities (Roberts & Lishman, 1984). Even so, it seems probable that those scanned are more likely to have clinical features suggestive of organic brain damage. However, it is hard to see how this could adequately explain the present pattern of results. Indeed, it has been suggested that the selection of a population at increased risk of cerebral trauma should facilitate the finding of an inverse relationship between family history and schizophrenia (Nimgaonkar *et al*, 1989).

Secondly, diagnoses in relatives were made using the family history method rather than by direct personal interview. It is well established that the family history method is highly specific but lacks sensitivity (Andreasen *et al*, 1986; Zimmermann *et al*, 1988). In the present study specificity was further improved by access to relatives' case notes for over 50% of probands with a family history of schizophrenia. Low sensitivity is likely to have operated to reduce differences between patients with and without a positive family history. Sensitivity can be improved by broadening the definition of positive family history to include those who have relatives with psychoses that do not fulfil diagnostic criteria for schizophrenia or affective disorder (Andreasen *et al*, 1986). However, even when this was done in the present study, an inverse correlation was not seen between family history and ventricular enlargement. In addition, those studies that have demonstrated such a relationship also employed the family history method (Reveley *et al*, 1984; Reveley & Chitkara, 1985; Cazullo *et al*, 1985; Turner *et al*, 1986; Owen *et al*, 1987).

Thirdly, there are limitations associated with classifying patients on the basis of psychopathology in relatives (see Lewis *et al* (1987) for discussion). Some family members will not have lived through, or even have reached, the age of risk for major psychiatric disorder. The main effect of this will be to increase further the number of probands incorrectly designated as having a negative family history. This is a weakness of the familial/sporadic strategy, and future studies should take this into account by examining the relationship between ventricular size and age-corrected morbid risk of illness in relatives. However, this artefact is common to previous studies that have demonstrated a difference between subjects with and without a positive family history. It is difficult to see why it should have selectively obscured such a finding in the present study, which has the advantage of larger numbers and greater statistical power.

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British Journal of Psychiatry (1989), **154**, 635–639

A Study of Factors Associated with Response to Electroconvulsive Therapy in Patients with Schizophrenic Symptoms

DAVID DODWELL and DAVID GOLDBERG

Seventeen patients with schizophrenic symptoms were assessed before and after ECT to elicit possible factors predictive of outcome. The strongest associations with good outcome were shown by short duration of illness and paucity of pre-morbid schizoid personality traits; significant associations were also shown by short duration of current episode, paucity of paranoid pre-morbid personality traits, and the presence of perplexity. The diagnosis of schizoaffective disorder was not related to outcome. Questionnaires completed by 16 patients after ECT showed their attitudes to be generally favourable to the procedure.

Although electroconvulsive therapy (ECT) was originally introduced as a treatment for schizophrenia, it soon became apparent that it was more successful in the treatment of severe depressive illness. With the advent of neuroleptic medication for schizophrenia, ECT became less frequently used, although no double-blind controlled trials were carried out. More recent interest has focused on the role of ECT in combination with neuroleptics. There have been three double-blind controlled trials, using operationally defined schizophrenics, which compared neuroleptics plus simulated ECT with neuroleptics plus real ECT. In each case, the real ECT group showed a statistically significant reduction in symptoms in the first two to four weeks, but the difference became statistically insignificant at later follow-up (12–28 weeks) (Taylor & Fleminger, 1980; Brandon *et al*, 1985; Abraham & Kulhara, 1987). The occurrence of any significant findings was surprising in view of the small groups involved (8–11 subjects), and the follow-up assessments took place after the treatment trial had ended, allowing the clinicians to prescribe an uncontrolled range of further treatments.

These modern trials suggest that ECT in combination with neuroleptics produces faster improvement than neuroleptics alone in non-chronic schizophrenia. It would be interesting to refine this viewpoint by determining firstly whether there are any individual symptoms that are especially susceptible to ECT, and secondly whether there are any clinical features that predict a good overall response to ECT.

Because ECT has proved so successful in the treatment of depressive states, it has often been assumed that depressive symptoms in schizophrenia should respond to ECT. However, the reports of Taylor & Fleminger (1980), Brandon *et al* (1985) and Abraham & Kulhara (1987) all indicate that depressive symptoms in the context of a schizophrenic illness are not especially responsive to ECT. Taylor & Fleminger (1980) reported that the most susceptible symptoms were delusions of control, delusions of reference, delusional mood, and thought interference. Similarly, Smith *et al* (1967) found ideas of reference to be the only symptom specifically affected. Kalinowsky & Worthing (1943) observed anecdotally that catatonic phenomena tended to respond to ECT.

The responsiveness of depressive illness to ECT has also suggested that schizoaffective disorders should be more responsive, a finding reported by Wells (1973). Other features associated with good outcome are absence of Schneider's first-rank symptoms (Koehler & Sauer, 1983), acute onset (Kalinowsky & Worthing, 1943; Lowinger & Huddleson, 1945), short duration of illness (Kalinowsky & Worthing, 1943; Lowinger & Huddleson, 1945; Herzberg, 1954), male sex (May, 1968), being married (Herzberg, 1954), and having at least a skilled or clerical occupation (Herzberg, 1954). Wittman's study (1941) includes some patients who did not receive convulsive therapy, but suggests that abnormal pre-morbid personality and poor pre-morbid function are associated with poor outcome whatever the treatment. Poor pre-morbid personality has been regarded as an important cause of poor outcome in schizophrenia generally, for self-evident reasons (Zubin *et al*, 1983). In addition to these clinical features, there is also a significant overlap between diagnoses of schizophrenia/schizoaffective disorder (by Research Diagnostic Criteria) and the clinical diagnosis of cycloid psychosis (Brockington *et al*, 1982), which is relevant because cycloid psychoses have been anecdotally reported to show a good response to ECT (Perris, 1974). A more detailed review of the literature is available in Dodwell (1983).

On the basis of the literature, it was hypothesised that in patients with schizophrenic symptoms, good outcome after ECT would be associated with fulfilment of diagnostic criteria for schizoaffective disorder and cycloid psychosis, with the presence of depressive symptoms, catatonic features and perplexity, with short duration of illness, with having been married at any time, and with the absence of schizoid or paranoid traits in the pre-morbid personality.

Method

The subjects referred for study were patients whom the medical staff believed to have schizophrenic symptoms, and who were prescribed ECT by their consultants. In order to be included in the study, the patients had to fulfil Research Diagnostic Criteria (RDC; Spitzer *et al*, 1980) for schizophrenia or schizoaffective disorder.

The patients were assessed before and after ECT using the Schedule for Affective Disorders and Schizophrenia – Change Version (SADS–C) of Spitzer & Endicott (1978). This scale is an abbreviated form of the SADS, and assesses 44 symptoms and signs over the previous week. It can be collated into seven subscales, as well as a total score. The four subscales used in the present study were depression, endogenous features of depression, anxiety, and psychotic features (delusions, hallucinations, disorganisation). In addition, the Global Assessment Scale (GAS; Endicott *et al*, 1976) was employed: this provides an overall measure of psychiatric symptoms and social function rated on a 100-point scale. The SADS–C and GAS were based on interviews with the patients, nursing observations, and details from the case notes. Further information collected included data necessary to make a diagnosis of cycloid psychosis according to the criteria of Cutting *et al* (1978).

Schizoid and paranoid traits in the pre-morbid personality were determined using criteria derived from ICD-9 (World Health Organization, 1978). Schizoid traits were defined as the presence of at least one out of the following four: withdrawal from social contact, autistic preference for fantasy or reserve, eccentricity or avoidance of competition, and incapacity to express feelings. Paranoid traits were defined as the presence of excessive self-reference, with or without one of the following four: sensitivity to setbacks and rebuffs, misperception of others as hostile or contemptuous, combative and tenacious sense of personal rights, and proneness to jealousy or self-importance. Personality traits were assessed after some improvement in acute symptoms had taken place, in order to reduce their contamination with features of the current illness. Also noted were demographic factors (age, sex, and marital status), concurrent medication, and the number of treatments producing a convulsion (as assessed by the psychiatrist present at ECT).

Four outcome assessments were used. The outcome in the first few weeks after ECT was assessed by the SADS–C psychotic subscale, the SADS–C total, and the GAS. A follow-up rating was obtained by reviewing the case notes of all the patients at least three months after the last ECT in the study. Patients were ranked according to the degree of supervision required, using the following nine categories: discharged on no treatment, out-patient well on no treatment, out-patient with neurotic or negative symptoms, out-patient with positive symptoms, hostel resident, day centre client, day hospital patient, intermittent in-patient, and continuous in-patient.

After the course of ECT was over, patients were asked to complete a short questionnaire about their experience of ECT and attitudes to it. The questionnaire items were derived from the work of Freeman & Kendell (1980).

Results

The total number of patients seen was 17. No suitable patients were withheld by clinicians because of the patient's clinical state, but some suitable patients were not referred to the study by accident. One patient refused to participate.

All the referred patients had at least two schizophrenic symptoms as defined by RDC: five fulfilled the criteria for schizophrenia, and the remaining 12 the criteria for schizoaffective disorder, depressed type. Ten patients also met Cutting's criteria for cycloid psychosis. The patients' ages ranged from 17 to 62 (median 37), and 13 were women. Nine patients were single, one was divorced and seven were married. All subjects were concurrently treated with neuroleptic medication. In terms of individual symptoms, nine patients were perplexed, and four had catatonic features. The length of illness was described in two ways, because of the nature of the disorders encountered. The total illness duration was assessed clinically, and was found to range from less than one month to 108 months (median 6). Many of the patients with chronic symptoms were prescribed ECT for a recent exacerbation of their symptoms, and this was referred to as the current episode duration, which ranged from less than one month to 36 months (median 3.5). Five patients had pre-morbid paranoid traits, and 11 had pre-morbid schizoid traits. The number of ECTs received ranged from 3 to 12 (median 6).

In terms of outcome on the GAS, seven patients scored under 40 (indicating major impairment in several areas), and the remaining ten scored over 50 (i.e. were not suffering from any serious symptoms or impairment in functioning that obviously required attention). At follow-up, six patients were asymptomatic, four were maintained as out-patients with symptoms, three were in hostels or day care, one had interrupted in-patient care, and three required continuous in-patient care.

The scores on the GAS, SADS–C total, and four SADS–C subscales (depression, endogenous features of depression, anxiety, and psychotic features) all showed a highly significant improvement after ECT (Wilcoxon signed-ranks statistic $t = 0–21.5$, $P < 0.005$ for all values). Simple outcome scores and the changes in scores before and after ECT were highly correlated (rho $= +0.82–+0.98$, $P < 0.001$ for all values), and so the simple outcome scores were used for further analysis.

The relationships between possible predictors and outcome measures are shown in Tables I and II.

TABLE I

Correlations between outcome and ranked pre-outcome measures

Pre-outcome measures	*Outcome measures*			
	GAS	*SADS–C 'psychotic' subscale*	*SADS–C total*	*Follow-up outcome*
SADS–C depression scale	−0.14	−0.14	+0.22	−0.36
SADS–C endogenous scale	−0.49*	−0.37	+0.03	−0.57**
SADS–C anxiety scale	−0.04	−0.04	+0.37	−0.14
SADS–C 'psychotic' scale	−0.25	+0.17	−0.07	−0.14
SADS–C total score	−0.20	−0.02	+0.25	−0.35
Length of illness	+0.59**	+0.41*	+0.36	+0.42*
Length of current episode	+0.45*	+0.30	+0.45*	+0.28
Number of ECTs	−0.04	+0.04	−0.20	—
Age	+0.11	+0.38	+0.07	+0.02
Number of paranoid traits	+0.19	+0.36	+0.44*	+0.24
Number of schizoid traits	+0.39	+0.61**	+0.12	+0.37

High score = bad outcome on outcome measures. Figures are values of Spearman's rank-order correlation coefficient.
*$P<0.050$. **$P<0.010$.

TABLE II

Associations between outcome and dichotomous pre-outcome measures

Pre-outcome measures		*Outcome measures*			
	n	*GAS*	*SADS–C 'psychotic' subscale*	*SADS–C total*	*Follow-up outcome*
Catatonic features	4	−1.42	−0.28	−0.85	−1.24
Perplexity	9	−1.20	−1.49	−2.07*	−1.20
Mood-congruent delusions/ hallucinations	11	−1.21	−1.61	−0.80	−2.26*
Schizoaffective psychosis	12	0.00	−0.95	+1.00	−1.00
Cycloid psychosis	10	−0.93	−0.83	+0.20	−1.51
Female	13	−2.15*	−2.15*	−1.36	−2.15*
Married/divorced	8	+0.53	−0.29	+1.25	−1.44
Anti-Parkinsonian agents	10	+0.68	+0.73	+0.05	+1.51
Benzodiazepines	7	+1.12	+0.10	+0.73	+1.81
Tricyclic antidepressants	3	+0.25	0.00	−0.94	−1.89
Lithium	3	−0.38	−0.31	−0.25	−0.38

Figures are values of Z obtained from the Mann-Whitney U test (although the probability was taken directly from tables of U): a negative value indicates that the presence of the feature is associated with a lower outcome score, i.e. better outcome.
*$P<0.050$.

The outcome scores showed no statistically significant relationship to the pre-ECT SADS–C depression, anxiety, and psychotic subscales, the SADS–C total score, the GAS score, the presence of catatonic features, the diagnoses of schizoaffective disorder or cycloid psychosis, or marital status. There was also no significant relationship between outcome scores and number of ECTs received, prescription of psychotropic medication (lithium, tricyclic antidepressants, benzodiazepines, and anti-Parkinsonian agents), or patient's age.

The statistically significant results are indicated in the tables. It has been assumed that measures predominantly related to the early outcome (GAS, SADS–C psychotic subscale, and SADS–C total) are likely to be measuring a specific effect of ECT, whereas measures related equally to both the early outcome and the follow-up outcome are more likely to be measuring good prognostic features that bear no specific relationship to ECT.

The tables show that length of illness, length of current episode, number of schizoid personality traits, number of paranoid traits, and the absence of perplexity are likely to be specifically related to prognosis after ECT. Mood-congruent delusions or hallucinations, female sex, and the SADS–C endogenous features of depression subscale are probably features of good general prognosis that are not specific to outcome after ECT.

Sixteen patients completed a questionnaire on their experience of and attitudes to ECT. Thirteen respondents felt that ECT had helped them, 12 agreed with the statement that ECT was a helpful and useful procedure, and the majority agreed that, if necessary, they would readily have ECT again. The patients' perceptions of benefit showed no statistically significant relationships with the SADS-C total or GAS outcome scores.

Discussion

The present study is the first study of the predictors of outcome after ECT in patients with operationally defined schizophrenic illnesses. Like the recent studies of the efficacy of ECT in schizophrenia (Taylor & Fleminger, 1980; Brandon *et al*, 1985; Abraham & Kulhara, 1987), its major weakness is the small number of patients. This is probably due to the currently unfashionable status of ECT in general (Bourgeois *et al*, 1982), and as a treatment for schizophrenia in particular (Pippard & Ellam, 1981). The commonest effect of small numbers is to produce a false negative result (type II error), a point which strengthens the significant findings reported in this study. However, small numbers also exaggerate the effects of individual variability, and because of increased random variation, a false positive result (type I error) may be generated (Newcombe, 1987). The most appropriate way of testing for this is to replicate the study on a new set of patients.

During the time of this study, it was unusual for patients with schizophrenic symptoms to be given ECT in the hospitals concerned. The patients were thus selected by the clinicians concerned. It was not possible to determine the basis of this selection, and the resulting sample may not be representative of schizophrenic patients in general. One should, therefore, be cautious in extrapolating these results to other groups of schizophrenic patients.

In a naturalistic clinical study of this type, it is difficult to determine which aspects of the total treatment package are the effective ones. All the subjects were in-patients, and thus receiving an important social treatment. They were all also receiving neuroleptic medication. Although impossible to ascertain accurately, no doubt some form of psychotherapy was administered whenever possible. A crude attempt to address this problem was made by contrasting the immediate outcome with status at follow-up, on the supposition that the former would be more strongly associated with ECT-specific effects than the latter. Using this approach, it was concluded that the good outcome associated with endogenous features of depression, female sex, and mood-congruent delusions or hallucinations, could have been due to non-specific effects. Leff & Wing (1971) found endogenous features of depression to predict good outcome in schizophrenics treated with neuroleptics but not ECT, which supports the view here that the good outcome associated with endogenous features of depression is not necessarily specific to ECT. Both Watt *et al* (1983) and Salokangas (1983) found better outcome in female schizophrenics receiving conventional treatment, which supports the view that the good prognosis in females is not specific to ECT. The implication that mood-congruent delusions and hallucinations indicate a good prognosis in patients with schizophrenic symptoms is consistent with the construct of psychogenic psychoses expounded by Strongren (1974), namely that these are psychoses which may appear similar to schizophrenia, but which often have comprehensible symptoms, and are characterised by a good prognosis. The finding is contrary to the study of mood-congruent delusions in depressive illness, which have been reported to be specifically responsive to ECT (Clinical Research Centre, 1984). However, it may be the case that both affective and schizophrenic illnesses with mood-congruent delusions and hallucinations are responsive to ECT and/or neuroleptic drugs, but not antidepressant drugs, which would account for the current findings.

The positive findings are generally consistent with the old literature. Good prognosis was found to be associated with shorter illnesses by Kalinowsky & Worthing (1943) and Lowinger & Huddleson (1945). Duration of current episode (included here as many patients had an acute-on-chronic disorder) has similar prognostic value, as one might expect. The finding that the number of schizoid or paranoid traits is related to poor prognosis is consistent with the report of Wittman (1941). Perplexity as a good prognostic factor is consistent with the view that cycloid psychoses (in which this is a frequent feature) respond well to ECT (Perris, 1974), and characteristically have a good prognosis (Leonhard, 1961). Although these features have been related to the outcome after ECT, there is no firm evidence that they are specific to outcome after ECT rather than general outcome after neuroleptic or other treatment. The International Pilot Study of Schizophrenia (World Health Organization, 1979) showed that longer duration of illness and poor pre-morbid psychosexual adjustment were both associated with longer initial illness.

The risk of a type II error due to the small number of subjects may apply to the present finding that affective features (SADS–C depression subscale, SADS–C anxiety subscale and diagnosis of schizoaffective disorder) are not related to good outcome, contrary to the report of Wells (1973), which suggested that depression was a predictor of good outcome in schizophrenics treated with ECT. On the other hand, the report of the International Pilot Study of Schizophrenia (World Health Organization, 1979) suggests that affective features are associated with good prognosis in schizophrenia, independent of ECT. The latter report would predict that, in the present study, affective features should have been associated with good outcome at follow-up, which was not the case. The present study also failed to find any association between catatonic features and good outcome after ECT, although various studies suggest that catatonic schizophrenia responds well to ECT (e.g. Hamilton & Wall, 1948; Ellison & Hamilton, 1949; Wells, 1973). However, catatonic symptoms are very non-specific (Kahlbaum, 1874; Gelenberg, 1976), and many patients diagnosed in the early studies as catatonic schizophrenics may in fact have had manic-depressive illnesses, or cycloid psychoses responding to ECT or recovering spontaneously.

The advances in psychiatry represented by reliable description of psychopathology and the advent of operationally defined diagnostic criteria have rendered suspect much of the old work on predicting which schizophrenics may respond to ECT. This field is therefore suitable for further scientific exploration; the present findings, both positive and negative, should be confirmed by replication of the study using a further patient group with larger numbers. Ideally, such a study should include double-blind allocation to ECT or simulated ECT, in order to ascertain which features predict a specific response to ECT and which are simply indicators of good prognosis in general.

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A Family Study of Two Subgroups of Schizoaffective Patients

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A family study was carried out in two groups of patients fulfilling RDC for schizoaffective disorder: in one, a full affective and a full schizophrenic syndrome were simultaneously present; in the other, affective and schizophrenic features appeared within a polymorphic and rapidly changing clinical picture, with depersonalisation/derealisation and/or confusion. In the first-degree relatives of patients of the former group, the risk of major psychiatric disorders was not significantly different from that of relatives of schizophrenics, whereas in the first-degree relatives of patients of the latter group a low risk for both schizophrenia and major affective disorders, and a relatively high risk for schizoaffective disorders, were observed.

The nosological status of schizoaffective disorders remains very uncertain. There are, in fact, at least five different hypotheses about the nature of these conditions (Maj & Perris, 1985): (a) they are variants of schizophrenia; (b) they are variants of major affective disorders; (c) they represent a 'third psychosis', distinct from both schizophrenia and major affective disorders; (d) they find their place in the intermediate part of a 'continuum', whose poles are represented by the typical forms of schizophrenia and manic-depressive illness; (e) they result from the simultaneous occurrence of a true schizophrenia and a true major affective disorder in the same patient.

In order to test the validity of these hypotheses, several family studies of schizoaffective probands compared with patients with schizophrenia and/or with major affective disorders have been carried out, although in only a small proportion of these investigations was the relatives' diagnoses made without knowledge of the probands' diagnoses and the age-corrected morbidity risks for the different disorders calculated. The studies by Mendlewicz *et al* (1980) and Baron *et al* (1982) suggested that schizoaffective disorders, defined according to Research Diagnostic Criteria (RDC; Spitzer *et al*, 1975), encompass a heterogeneous group of conditions, part of which may be related to major affective disorders and part to schizophrenia. The Kraepelinian 'binary' paradigm was especially supported by Baron *et al*'s finding of an excess of schizophrenia in the relatives of 'mainly schizophrenic' schizoaffectives, and of an excess of affective disorders in the relatives of 'mainly affective' schizoaffectives. On the other hand, the reports by Gershon *et al* (1982) and by Abrams & Taylor (1980) supported the view that RDC schizoaffective disorders are usually variants of major affective disorders and, more precisely, correspond to the most 'virulent' forms of these conditions. It should be emphasised, however, that in Gershon *et al*'s study a complete recovery between the episodes was required as a selection criterion, while in Abrams & Taylor's investigation only schizomanics were considered: it is possible, therefore, that in patient samples recruited by these authors the 'mainly affective' subtype of schizoaffective disorders was over-represented.

Overall, the results of family studies speak in favour of an interpretation of schizoaffective disorders as variants of either schizophrenia or major affective disorders, with a greater frequency of cases related to affective disorders. This leaves two questions unanswered. First, may we conclude that *all* schizoaffective disorders are variants of either of the major psychoses? Indeed, some research findings (Maj, 1988) seem to indicate that there is a subgroup of schizoaffective patients who escape such dichotomy, in whom affective and schizophrenic features frequently appear within a more complex polymorphic and rapidly changing clinical picture, with depersonalisation/derealisation and/or confusion (Perris, 1974; Pull *et al*, 1983). How should these cases be interpreted? Do they represent a 'third' psychosis?

The second question arises from the observation that RDC for schizoaffective disorders, which have been used in the great majority of family studies, require the occurrence of a *full* affective syndrome together with at least *one* of a series of schizophrenic-like symptoms. The emphasis, therefore, is on the affective component, which may have conditioned the results of the investigations. Thus, the question is, what is the risk for major psychiatric disorders

TABLE I
Socio-demographic and historical features of the schizoaffective patients

Variable	*Group (a) (n = 20)*	*Group (b) (n = 18)*
Educational level: years of schooling, mean ± s.d.	10.2 ± 4.5	10.8 ± 5.6
% married	30.0	27.7
Age at onset: years, mean ± s.d.	27.5 ± 5.0	24.8 ± 5.4
Duration of illness: years, mean ± s.d.	8.5 ± 4.0	8.3 ± 4.5
No. of admissions: mean ± s.d.	1.8 ± 1.6	1.9 ± 1.0
History of perinatal complications: % positive	5.0	16.7

in the relatives of patients showing simultaneously a full affective and a full schizophrenic syndrome? Is there any evidence of a mixed heredity? The present study was designed to provide an answer to the above questions.

Method

Subjects

The study was carried out in the following samples of patients. (a) Twenty subjects (7 men, 13 women, aged 26–49 years, mean ± s.d. 36.1 ± 6.2) fulfilling RDC and the cross-sectional criteria of Maj & Perris (1985) for schizoaffective disorder:

- (i) Manic subtypes: 1–3 are required (all symptoms are defined according to the comprehensive Psychopathological Rating Scale (CPRS; Åsberg *et al*, 1978):
  - (1) Presence of at least three of the following symptoms: feeling controlled, or disrupted thoughts, or ideas of persecution; commenting voices, or other auditory hallucinations, or hallucinatory behaviour; lack of appropriate emotion; withdrawal; incoherent or empty speech; mannerisms and postures.
  - (2) Presence of persistent and prominent elation.
  - (3) Presence of at least five of the following symptoms: reduced sleep; increased sexual interest; ideas of grandeur; distractibility; pressure of speech; flight of ideas; overactivity; increased energy; disinhibition.
- (ii) Depressive subtype: 1–3 are required:
  - (1) As for manic subtype.
  - (2) Presence of persistent and prominent sadness.
  - (3) Presence of at least six of the following symptoms: inability to feel; pessimistic thoughts; suicidal thoughts; lassitude, or fatiguability; concentration difficulties, or failing memory; reduced appetite; reduced or increased sleep; reduced sexual interest; slowness of movement, or agitation; negative self-evaluation; social withdrawal.

(b) Eighteen subjects (8 men, 10 women, aged 24–46 years, mean ± s.d. 33.9 ± 5.2) fulfilling both RDC for schizoaffective disorder, and the criteria of Pull *et al* (1983) for *bouffée délirante*:

- (i) Acute onset.
- (ii) All of the following: delusions and/or hallucinations of any type; depersonalisation/derealisation and/or confusion; depression and/or elation; symptoms vary from day to day, even from hour to hour.
- (iii) Not due to any organic mental disorder, alcoholism or drug abuse.

(c) Twenty-five subjects (10 men, 15 women, aged 25–48 years, mean ± s.d. 34.9 ± 8.1) meeting RDC for schizophrenia; (d) 25 subjects (10 men, 15 women, aged 25–49 years, mean ± s.d. 35.4 ± 7.5) meeting RDC for bipolar I disorder. Patients in groups (a) and (b) were consecutively recruited from the out-patient facilities of the First Psychiatric Department of Naples University, and patients in groups (c) and (d) were recruited from the in-patient and out-patient facilities of the same department, so as to obtain a similar age distribution and sex ratio.

The socio-demographic, historical and clinical features of the schizoaffective patients are summarised in Tables I and II. The following case reports give examples of each schizoaffective patient group.

Case reports

Case 1, group (a)

A 26-year-old girl was brought by her parents to our department. She was depressed and tearful, her speech incoherent. She had delusions of being controlled and other bizarre ideas (having snakes in her abdomen), intense feelings of guilt and auditory hallucinations (a voice repeating her thoughts), and reported a decrease of sleep and appetite. The patient had attempted suicide by a superficial wrist cut some days previously. According to her parents, there was no previous psychiatric history. As to pre-morbid personality, the girl was described as timid and reserved, with a small circle of friends, and very few male relationships. During the months preceding the onset of the episode, she had been engaged to be married for the first time, but she had soon broken the engagement because, she said, her fiancé was unemployed. The patient was admitted and treated with haloperidol (up to 10 mg daily) and amitriptyline (up to 100 mg daily). She was discharged, considerably improved, after two months.

Case 2, group (b)

A 24-year-old girl was brought by her mother to our department. She was elated, restless, and talked incessantly. Grandiose and persecutory ideas were manifested, but they were fragmentary and rapidly changing. Occasionally, she complained that someone interfered with her thinking. Perplexity and misidentifications were clearly present, and feelings of unreality were sometimes expressed. There was no evidence of hallucinations. Decreased sleep, sexual disinhibition, and eating of improper things were reported.

TABLE II
Data concerning the first CPRS assessment in schizoaffective patients

Selected CPRS items	% with a rating of at least 2	
	Group (a) (n = 20)	Group (b) (n = 18)
Sadness	50.0	55.5
Elation	50.0	45.5
Depersonalisation	5.0	16.7
Derealisation	5.0	11.1
Feeling controlled	40.0	27.8
Disrupted thoughts	35.0	27.8
Ideas of persecution	65.0	50.0
Ideas of grandeur	40.0	33.3
Delusional mood	10.0	38.9
Commenting voices	25.0	22.2
Other auditory hallucinations	65.0	55.5
Visual hallucinations	15.0	33.3
Lack of appropriate emotion	25.0	11.1
Perplexity	0	22.2
Disorientation	0	22.2
Incoherent speech	35.0	22.2
Overactivity	40.0	33.3
Slowness of movement	35.0	27.8
Agitation	20.0	55.5

According to her mother, there was no previous psychiatric history. The onset of the episode had been acute, after surgery for appendicitis. Pre-morbid personality was described as characterised by difficulty in tolerating anyone regarded as 'authoritative', and excessive sensitivity to frustrations. The patient was admitted and treated with haloperidol (up to 12 mg daily), lithium carbonate (up to 900 mg daily) and diazepam (up to 10 mg daily). She completely recovered and was discharged after one month.

Data collection

All consenting first-degree relatives of the probands were directly interviewed, using the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L; Endicott & Spitzer, 1978). Interviewers were blind to the proband's diagnosis. Direct interview was supplemented by the family history, collected from all available sources (other family members, health care providers, hospital records). The information concerning each relative was reviewed by an independent clinician, who assigned a 'best-estimate' diagnosis according to RDC. Out of 483 first-degree relatives, 349 could be interviewed. In the remainder, interview was not possible because of death, geographical distance, or refusal to participate. The proportion of relatives who could not be interviewed was almost the same in the four patient groups.

Data analysis

The risk for major psychiatric disorders was determined by the method of Weinberg (1925). The following risk periods were used: 15–70 years of age for major affective disorders, 15–50 years for schizophrenia, and 15–70 years for schizoaffective disorders. The χ^2 test with Yates' correction was used for statistical analysis.

Results

As shown in Table III, the relatives of group (a) patients had a significantly higher risk for schizophrenia, and a significantly lower risk for major affective disorders, compared with the relatives of bipolars, whereas they did not differ significantly from the relatives of schizophrenics. On the other hand, the relatives of group (b) schizoaffectives had a risk for schizophrenia significantly lower than the relatives of schizophrenics and not different from the relatives of bipolars, a risk for major affective disorders significantly lower than the relatives of bipolars and not different from the relatives of schizophrenics, and a risk for schizoaffective disorders which was higher, but not significantly, than the relatives of both schizophrenics and bipolars.

Discussion

The data concerning group (a) schizoaffectives confirm that the research findings obtained using RDC may be biased by the emphasis put in these criteria on the affective component of schizoaffective phenomenology. When patients showing simultaneously a full affective and a full schizophrenic syndrome are studied, the risk for major psychiatric disorders in first-degree relatives is not different from that of schizophrenics. This finding is in line with the outcome data reported by Williams & McGlashan (1987) in a similar patient sample, and supports the hierarchical relationship between the schizophrenic and the affective syndrome proposed by Jaspers (1962), which has been overturned in DSM-III (American Psychiatric Association, 1980). On the other hand, it is important to stress that no evidence of a mixed heredity was observed in these patients with both a full affective and a full schizophrenic syndrome, which speaks against the 'coincidence of two diseases' hypothesis.

The interpretation of the data concerning group (b) schizoaffectives is less clear. The first-degree relatives of these patients showed a low risk for both schizophrenia and major affective disorders, and a low total risk for major psychiatric disorders. The risk for schizoaffective disorders was higher than in the relatives of any other patient group, but not significantly. Moreover, in this group a history of perinatal complications was relatively frequent

TABLE III

Morbidity risk for major psychiatric disorders in first-degree relatives of schizoaffectives, schizophrenics, and bipolars

Probands	*No. of relatives interviewed*	*Relatives*								
		Schizophrenia			*Major affective disorders*[2]			*Schizoaffective disorders*		
		Sample size[1]	n	*Risk (%)*[3]	*Sample size*[1]	n	*Risk (%)*[3]	*Sample size*[1]	n	*Risk (%)*[3]
Group (a)	81	49	3	6.1*	45.5	3	6.6*	45.5	1	2.2
Group (b)	76	47.5	0	0**	44.5	2	4.5*	44.5	2	4.5
Group (c)	95	55.4	5	9.0*	52.0	2	3.8*	52.0	1	1.9
Group (d)	97	57.0	0	0	53.0	7	13.2	53.0	1	1.9

1. Adjusted for period of risk.
2. Bipolar cases in relatives were one for groups (a–c), and four for group (d).
3. Overall group difference at $P<0.01$ by χ^2.

*Significantly different with respect to relatives of group (d), $P<0.05$.

**Significantly different with respect to relatives of group (c), $P<0.05$.

(16.7% v. 5% in group (a), 8% in group (c), and 4% in group (d)). One could cautiously speculate, therefore, that this subgroup of schizoaffective disorders includes a high proportion of forms not related to either of the major psychoses, part of which may breed true (as suggested by the relatively high risk for schizoaffective disorders in patients' relatives), and part of which may arise from environmental factors (as suggested by the low total risk for major psychiatric disorders in patients' relatives and by the high frequency of perinatal complications). The Japanese literature on 'atypical psychoses' and their relationship to epilepsy (Mitsuda, 1965) may be relevant in this last connection.

Thus, according to our data (which should be regarded as preliminary, owing to the small size of the patient samples), it seems that not *all* schizoaffective disorders are variants of either schizophrenia or major affective disorders. A better characterisation of the schizoaffective forms which escape the Kraepelinian binary paradigm, and a clarification of their nosological nature, appear to be major focuses for future research.

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A Comparison of In-patient and Out-patient Prescribing

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The prescribing of psychotropic medication to 96 attenders at a lithium clinic was compared with their prescriptions while in-patients. As out-patients, they received fewer psychotropic drugs fewer times a day. This suggests that psychiatrists do not adopt intransigent stances in favour of polypharmacy and irrational psychotropic prescribing, as previous studies have implied. Caution is advised before attributing apparently irrational prescribing to bad clinical practice, or advocating remedial action aimed at changing the habits of prescribers.

Prescribing patterns for psychotropic drugs have been reported from several countries, including England (Michel & Kolakowska, 1981), the USA (Sheppard *et al*, 1969), Israel (Yosselson-Superstine *et al*, 1979), and Finland (Hemminski, 1977). Researchers have generally been critical of psychiatrists' prescribing habits, particularly the incidence of polypharmacy (the concurrent use of two or more psychotropics), excessive frequency of administration, irrational combinations of pharmacological agents, and their appropriateness (Laska *et al*, 1973; Hemminski, 1977; Superstine *et al*, 1979; Michel & Kolakowska, 1981; Edwards & Kumar, 1984; Clark & Holden, 1987; Muijen & Silverstone, 1987), as well as inadequate dosage (Kotin *et al*, 1973). Authors have, correctly, pointed out the hazards of polypharmacy, and the advantages of a pharmacologically more rational use of psychotropic medication (Ayd, 1973; Clark & Holden, 1987).

Although these studies have given the impression of universally poor pharmacological practice, there has been a considerable variation between individual prescribers and hospitals (Winstead *et al*, 1976; Yosselson-Superstine *et al*, 1979; Muijen & Silverstone, 1987). Only occasionally have patient and illness variables been commented on in association with differential prescribing patterns (Sheppard *et al*, 1969; Merlis *et al*, 1970, 1972), being relatively ignored compared with the attention paid to the prescribers' characteristics and attitudes (Merlis *et al*, 1972; Winstead *et al*, 1976), which are usually seen to be responsible for differential and irrational practice. This is exemplified by Hemminski's (1975) review of the factors affecting drug prescribing, which focused entirely on characteristics of the prescriber, with no reference to the effects of the patient or illness.

Undoubtedly contributing to the variation in findings are the considerable methodological problems (Priern *et al*, 1978). Different populations in different clinical settings have been compared, including acute, chronic and day patients. Functional and organic disorders are not distinguished, resulting in schizophrenic, affective and organic psychoses, neuroses, personality disorders, and even mental handicap being treated as a single group, yet they are not comparable from a management point of view.

Most clinicians would claim that they do not prescribe without reason or expected benefit, and Morgan & Gopalaswamy (1984) suggested they could account for 98.5% of their apparently illogical prescribing by patient and clinical context.

The studies do provide useful descriptive data about prescribing practices (Priern *et al*, 1978), and serve as a useful form of audit (Edwards & Kumar, 1984; Clark & Holden, 1987). It must, however, be realised that without detailed infomation regarding clinical context, a prescribing survey can only demonstrate evidence of pharmacological rationale and prevalence of practices, but not the appropriateness of specific treatments.

To date, studies have concentrated on in-patient populations, whereas psychiatric care is predominantly on an out-patient basis. But, if enduring characteristics of the prescriber are the sole or major determinants of psychotropic prescribing, the same questionable practices ought to be evident when the same patients are treated in different settings. To test this hypothesis the present study aimed (a) to record psychotropic prescribing in an out-patient population, (b) to compare this with the same population treated while in-patients, and (c) to consider the relationship between certain clinical variables relating to the course of illness and out-patient prescribing.

Method

It was necessary to select a diagnostically definable out-patient population, preferably with an accepted pharmacological treatment, who had also required in-patient care for the same illness. Diagnostic homogeneity was felt to be important because the more heterogeneous the patients studied, the less uniform would be expected management (Priern *et al*, 1978). Attenders at a lithium clinic were considered a suitable population to fulfill these requirements.

All patients attending the lithium clinic of a district general hospital for their routine follow-up appointments during a six-month period were approached by the investigator. The patients were seen on the day of their appointment, after their interview with the clinic doctor. Each patient was seen only once for the purpose of the study. They were asked for details of their current psychotropic medication, including name of drug, dosage, and the frequency with which they took medication during the day. 'As-required' medication was included only if taken daily during the preceding week. Patients' age, and marital and occupational status were also recorded.

The following information was then obtained from a thorough case-note review: case-note diagnosis, duration of illness (from first in-patient admission), number of admissions with illness, duration of treatment with lithium, time since last discharge from in-patient care, and current plasma lithium level.

The details used for in-patient medication were those recorded in the last discharge letter to the general practitioner, and the frequency of daily dosage was taken as that recorded on the final in-patient prescription chart.

In order not to influence prescribing, the patients and clinic doctor were told that the purpose of the study was to investigate prescription costs, and therefore patients were also asked the cost of their last prescription and benefits which might exempt them from prescription charges. This information was not retained for analysis.

No attempt was made to assess the patient's mental state.

Results

Of 107 patients with appointments at the clinic, two failed to attend, five required in-patient admission and consequently did not attend, and three who attended were not taking lithium (one discontinued owing to recent physical illness, one discontinued of his own accord, and one was attending for monitoring of carbamazepine). These ten patients were excluded.

Of the remaining 97 patients, the case-note diagnoses were bipolar affective disorder ($n = 67$), unipolar depression ($n = 21$), schizoaffective disorder ($n = 8$), and schizophrenia ($n = 1$). Schizophrenia was excluded to maintain diagnostic homogeneity, but schizoaffective disorder was included as it resembles affective disorders in terms of course of illness (Rosenthal *et al*, 1980; Pope *et al*, 1980) and response to lithium (Goodnick & Meltzer, 1984; Maj, 1984), although problems with the nosological status of this group are accepted (Brockington & Leff, 1979; Tsuang & Simpson, 1984).

Ninety-six patients were, therefore, included for analysis (Table I).

TABLE I

Patient characteristics of the 96 patients studied

	No. of patients
Diagnoses	
bipolar	67
unipolar	21
schizoaffective	8
Sex	
male	32
female	64
Marital status	
married	55
single	17
divorced	12
separated	2
widowed	10
Occupation	
employed	19
unemployed	52
pensioner	25
Age: years	Mean 53.3 (s.d. 13.3, range 24–85)
Duration of illness:	Mean 18.4 (s.d. 9.9, range 1–47)
Time on lithium:	Mean 6.9 (s.d. 4.6, range 1–16)
No. of admissions:	Mean 6.7 (s.d. 5.3, range 1–33)
Time since discharge: years	Mean 4.4 (s.d. 4.5, range 0.1–17)
Plasma lithium level: mmol/l	Mean 0.75 (s.d. 0.2)
Lithium dose: mg/day	Mean 870

Current medication

All patients were receiving lithium in a single nightly dose (see Table II). The most commonly prescribed group of drugs other than lithium was tricyclic antidepressants, given to 34. Of the 28 patients taking oral neuroleptics, one patient was taking two different neuroleptics (compared with three patients in the in-patient sample). Five patients were receiving a depot preparation (all with a diagnosis of schizoaffective disorder), none of whom took an oral neuroleptic. Of those on neuroleptics, 30% received an anticholinergic agent, and while 80% on depot forms received anticholinergics only 21% on oral forms did so.

The most commonly prescribed antidepressant was dothiepin (43% of those on antidepressants), and the most popular neuroleptic was thioridazine (70% of those on neuroleptics).

TABLE II
Medication prescribed

	As out-patients	*As in-patients*	*McNemar's test*	P
No. of psychotropics[2]				
1	31	12		
2	30	32		
3	22	33		
4	10	14		
5	3	4		
Neuroleptics[3]	28	48	13.884	0.001
Tricyclics	34	45	3.682	0.1
Monoamine-oxidase inhibitors	3			
Benzodiazepines	5			
Hypnotics	25	22	0.5	0.5
Carbamazepine	4			
Tryptophan	2			
Anticholinergics	10	20	16.2	0.001
Frequency of daily dosage[4]				
nocte	65	34		
b.d	15	15		
t.d.s.	13	28		
q.d.s.	3	18		

1. $n = 95$, as one out-patient had not attended as an in-patient.
2. χ^2 (2 d.f.) = 17.49, $P < 0.001$.
3. Includes five on depot preparations.
4. χ^2 (2 d.f.) = 30.64, $P < 0.0001$.

TABLE III
Comparison of patients taking lithium only and those receiving polypharmacy

	Lithium only	*Poly-pharmacy*	P
n	31	65	
Mean age: years	51.4	53.9	NS[1]
% bipolar	77.4	66.2	NS[2]
% male	45	28	NS[2]
% married	65	55	NS[2]
% employed	38	18	NS[2]
Mean duration of illness: years	16.52	19.47	NS[1]
Mean time on lithium: years	6.7	7.0	NS[1]
Mean no. of admissions	4.9	7.6	<0.01[1]
Mean time since discharge: years	5.7	3.7	<0.05[1]
Mean no. of admissions since taking lithium	0.83	2.57	<0.0027[1]
Mean no. of admissions before taking lithium	4.07	5.0	NS[1]

1. *t*-test.
2. χ^2 with Yates correction.

When comparing the major drug groups prescribed to unipolar and bipolar patients, there were no statistically significant differences, although there was a tendency for more unipolar patients to receive antidepressant medication and more bipolar patients to receive neuroleptic, anticholinergic and hypnotic medication (analyses using χ^2 with Yates' correction).

Current v. discharge medication

Details of medication at the time of last discharge are also shown in Table II. Significantly fewer out-patients received psychotropics prescribed with a reduced frequency of administration. When individual drug groups were analysed separately, significant reductions were found in out-patients for neuroleptics and anticholinergics. The prescribing of hypnotics increased following discharge, although this was not statistically significant, and antidepressants showed a non-significant reduction. A comparison of prescriptions for unipolar and bipolar disorders at the time of last discharge revealed that neither total number of drugs nor frequency of administration differed between the two groups.

Illness variables

Duration of illness, time on lithium, number of admissions, time since last in-patient discharge, and plasma lithium level were empirically considered factors which might affect prescribing. An analysis of the correlation between the number of psychotropics taken and each factor separately was performed. Eight patients had to be excluded from this part of the analysis because their complete medical records were not available, leaving 88 subjects.

There was no significant correlation for plasma lithium level ($r = +0.054$), duration of illness ($r = +0.052$), or duration of treatment with lithium ($r = +0.049$), and this remained so when bipolar patients were considered separately. The number of in-patient admissions showed a significant positive correlation with number of psychotropics taken ($r = +0.232$, $P < 0.05$), and time since last discharge a significant negative correlation ($r = -0.208$, $P < 0.05$). With the exclusion of one unipolar subject, the latter correlation increased ($r = -0.350$) to become significant at the $P < 0.001$ level.

Considering the bipolar group separately produces a correlation for number of psychotropics with number of admissions of $r = +0.399$ ($P < 0.01$), and with time since last discharge of $r = -0.349$ ($P < 0.01$).

Lithium only v. polypharmacy groups

There were no significant differences between patients taking lithium only and those receiving polypharmacy in terms of age, sex, number of bipolar patients, proportion employment, or marital status (Table III). The lithium-only group had required fewer admissions ($P < 0.01$), particularly since receiving lithium ($P < 0.0027$), and had been out of hospital longer ($P < 0.05$). It also included more patients who had not required admission at all since taking lithium ($\chi^2 = 4.706$, $P < 0.05$), even though there was no difference between the two groups in terms of duration of treatment with lithium, duration of illness, or number of admissions before lithium prophylaxis.

At the time of last discharge, the lithium-only group had more often received lithium only ($\chi^2 = 5.573$, $P < 0.02$) and less often received hypnotics (χ^2 with Yates' correction = 8.678, $P < 0.01$), but they did not differ in receipt of neuroleptics, anticholinergics, or antidepressants.

Discussion

The results show clearly that in-patient and out-patient prescribing to this group of patients are distinctly different, with a highly significant reduction in polypharmacy and frequency of daily dosage received by patients attending the clinic. This suggests that prescribers give consideration to changing clinical condition, and do not adopt intransigent stances in favour of polypharmacy and irrational pharmacotherapy. It is possible that clinicians intrinsically behave in very different ways when treating the in-patient and out-patient populations, but a preferred explanation is offered that variables relating to the patient, illness, course of illness, and clinical context are responsible for the differences seen. There may be a number of factors operating to influence the prescribers' decisions, but if the only variables were the attitudes, characteristics, and idiosyncracies of the prescribers themselves, one might expect to find evidence of consistently irrational habits in different clinical circumstances when considering the same patients receiving treatment for the same illness from the same clinical team. Prescribing is a complex, dynamic process, of which the prescriber is but one element, and the previous emphasis attributing all pharmacological irrationality to pharmacologically unaware clinicians is a gross oversimplification. In-patients represent an atypical psychiatric population, including the most severely disturbed and refractory cases, and prescribing in this setting cannot be taken as representative of prescribers' habits, nor can it be generalised to other situations.

In this study there was a clear association between polypharmacy and certain clinical variables relating to the course of illness. The significant positive correlation of degree of out-patient polypharmacy with number of patient admissions may simply reflect the prescribers' reluctance to reduce the medication of patients who relapse frequently, or may indicate the presence of patients who have responded poorly to lithium monotherapy. The latter possibility is supported by the evidence that patients receiving lithium only had required significantly fewer admissions than the polypharmacy group, particularly since receiving lithium prophylaxis, even though both groups had received lithium for comparable periods of time (Table III). The negative correlation between degree of polypharmacy and time since last discharge suggests that prescribers attempt to reduce medication over time as patients remain well, although it is not possible to know how much patients themselves initiate this change. It should be noted that patients relapsing frequently are likely to have been out of hospital for a shorter time, and these two variables are, therefore, unlikely to be independent.

The reduced use of neuroleptics in the out-patient sample may reflect their use in acute hypomania (which would be over-represented in the in-patient sample) or as an adjunct in the treatment of agitated or delusional depression (Spiker *et al*, 1985), similarly likely to be more common in the in-patient group. However, as only 11% received a combination of antidepressant and neuroleptic at discharge, differing little from the 8% receiving them in the out-patient clinic, this might favour the former interpretation.

As expected, anticholinergic use declined with decreased prescribing of neuroleptics, with only 30% of those taking neuroleptics as out-patients receiving an anticholinergic agent (39% at discharge). This compares favourably with the prevalence of neuroleptic/anticholinergic combinations emphasised by other studies (Laska *et al*, 1973; Michel & Kolakowska, 1981; Edwards & Kumar, 1984; Muijen & Silverstone, 1987; Clark & Holden, 1987). Although often highly criticised, the correct use of anticholinergic drugs continues to arouse conflicting opinions (Orlov *et al*, 1971; McClelland *et al*, 1974; Rifkin *et al*, 1978), with even eminent specialists divided on correct practice (Dorsey *et al*, 1979).

The prescribing of antidepressant and neuroleptic drugs to this out-patient group was pharmacologically more rational, at least with regard to frequency of dosage, than that seen with the in-patients, with 85% of antidepressants prescribed in a single nightly dose, compared with 53% of in-patient antidepressants. Neuroleptics were taken only at night by 43% of the out-patients but only 10% of in-patients.

The notion that psychotropic drugs are prescribed 'irrationally' has led to the conclusion that the prescribers' habits need to be changed, and a number of interventions have been proposed: greater education in psychopharmacology (Herxheimer, 1976; Clark & Holden, 1987), an increase in the number of clinical psychopharmacologists (Herxheimer, 1976; Muijen & Silverstone, 1987), increased control over clinicians' prescribing (Hemminski, 1975), more advice from pharmacists

(Chien *et al*, 1978; Yosselson-Superstine *et al*, 1979), and peer-group review (Diamond *et al*, 1976).

Muijen & Silverstone (1987) suggest the presence of a clinical psychopharmacology department was responsible for more 'rational' prescribing in one of their three hospitals surveyed, although there was no adequate control group. Chien *et al* (1978) claimed that a pharmacist's intervention was effective in rationalising prescribing when comparing two dissimilar out-patient groups treated in dissimilar out-patient facilities. Ellenor (1977) made similar claims when studying a group of in-patients with mental handicap, where 80% of the subjects were severely or profoundly retarded, findings difficult to extrapolate to adult psychiatry. Diamond *et al* (1976) purported to show that peer-group review improved prescribing in an out-patient clinic over 18 months, but again there was no control group. The results I have reported clearly show considerable changes to more rational prescribing on patient discharge, without any intervention. The differences found between in-patient and out-patient prescribing would not support the latter part of Diamond *et al*'s (1976) assertion that "unfortunately the chemotherapy of our hospitalised patients still seems to be rooted in polypharmacy; this carries over and introduces problems in out-patient medication maintenance".

Caution is advised before accepting that research has established evidence of inappropriate prescribing, or that interventions aimed at changing prescribers' practices are effective, beneficial, or even necessary, until adequately performed controlled studies provide this evidence. I would agree with Priern *et al* (1978) when they contend that "recommendations for remedial action based on the survey findings are, at best, premature". This becomes increasingly relevant with the escalating demands for audit (Smith, 1987). Clinicians' prescribing performance will be compared with others (or even norms), and if the complexities of the prescribing process are not appreciated, quite unjustifiable interpretations may result. A task force of the American Psychiatric Association (Dorsey *et al*, 1979) produced criteria for screening psychotropic prescribing, with the aim of establishing a nationwide comparability of care, and the difficulties, and perhaps undesirability, of dictating prescribing was demonstrated by their need to emphasise that they should be subject to adaptation based on "differences in populations, clinical practices, resources or professional judgement". They recognised "few absolute contraindications" in psychopharmacology, and accepted the value of drug combinations, i.e. polypharmacy.

Polypharmacy is undesirable when it confers no benefit on the patient, but the term has also come to imply bad practice. Many drug combinations have been shown to be effective in individuals with affective disorders (Worrall *et al*, 1979; De Montigny *et al*, 1981; Nelson & Byck, 1982; Heninger *et al*, 1983; Barker & Eccleston, 1984; Spiker *et al*, 1985; Price *et al*, 1985), and these offer individuals the chance of recovery from what may otherwise be protracted and disabling illnesses. A significant proportion of patients fail to respond to conventional monotherapy, and it is often left to empiricism to provide methods of relieving distress.

There are few categorical statements in the care of the mentally disordered, and the maxim of treatment must be to do good and not just look good: "Rigid application of pharmacologic 'rules' tends to ignore the complexity and variability involved in patient care . . . the use of drug combinations doesn't necessarily establish that a person is receiving inferior care" (Kimball & Glass, 1983).

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The Relationship Between Depression and Hopelessness

Implications for Current Theories of Depression

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In both Beck's cognitive theory of depression and Brown & Harris's sociopsychological model, hopelessness is given unwarranted universality and centrality. Empirical evidence contradicting this element of the two theories has been ignored, and two new investigations are presented which suggest the existence of 'non-hopeless' depression. A more complete account of the heterogeneous nature of depression is now required.

It is widely accepted that hopelessness is a typical feature of depression. Early empirical studies such as that of Grinker *et al* (1961), Pichot & Lempérière (1964), and Beck (1967) all found hopelessness and/or pessimism to be not merely a typical, but an important feature of the depressive constellation. However, not one of these studies would indicate that hopelessness is always and necessarily an element in depressive disorder. For example, Beck (1967) found that 78% of his 50 depressed patients reported a negative outlook, implying that 22% did not.

In the 1960s, at the same time as these early empirical studies were being reported, there was an awakening of interest in the construction of psychological theories of the origins of depression. It is argued here that in a number of the theoretical accounts published in the 1960s and 1970s, and certainly in the most influential of these theories, hopelessness is accorded unwarranted centrality and universality. Empirical data which have a bearing on the relationship between hopelessness and depression have been neglected in the cause of theoretical neatness and cogency.

It should be pointed out that there is some inconsistency in the usage of the term 'hopelessness' in the research literature. For example, pessimism is often used interchangeably with hopelessness (Minkoff *et al*, 1973; Beck *et al*, 1974*a*; Bernard, 1977). 'Negative expectancies' is a term also used by Beck as synonymous with hopelessness/pessismism. Although it could be argued that these terms have different and distinct meanings, for the purposes of this paper 'hopelessness', 'pessimism', and 'negative expectancies' will be taken to refer to the same set of psychological phenomena.

Thus, the definition of hopelessness employed in this paper refers to the person's own negative thoughts and feelings about their future. This corresponds, more or less, to the way the concept appears to be defined by major theorists in the area. It would not necessarily correspond to popular usage.

Theoretical approaches

Two theoretical approaches are examined in detail: Beck's cognitive theory of depression (Beck, 1967; Beck & Rush, 1978), and Brown & Harris's (1978) sociopsychological model of depression. There are other theories in which hopelessness is seen to have a critical aetiological role in the development of depression. For example, Lichtenberg (1957) argues that depression can be seen as "a manifestation of felt hopelessness regarding the attainment of goals when responsibility for the hopelessness is attributed to one's personal defects."

Stotland (1969) takes the view that the individual's hopelessness about important goals results initially in anxiety, but that if the individual lessens the importance of the goal, he then tends to become depressed, apathetic, and withdrawn. Thus Stotland sees hopelessness as one step removed from depression, but as a crucial step in the sequence leading to it.

Melges & Bowlby (1969) also see hopelessness as a defining characteristic of depression. The typical depressive (a) believes skills and plans of action are no longer effective for reaching his goals, (b) sees failures as due to his own incompetence so that he must rely more on others, and (c) deems his previous involvements in long-range goals to have met with numerous frustrations and failures. Points (b) and (c) could be seen as relating more to helplessness than hopelessness, but the authors see all three points as features of the type of hopelessness that leads to depression.

In their work following the revision of the 'learned helplessness' (LH) model of depression, Seligman, his co-workers, and other researchers working from the LH perspective have placed increasing emphasis on the role of hopelessness in depression (Abramson *et al*, 1978, 1980; Weiner & Litman-Adizes, 1980; Hollon & Garber, 1980). To quote Abramson *et al* (1980): "Affective changes result from the expectation that bad outcomes will occur and not from their expected uncontrollability". Weiner & Litman-Adizes (1980) point out: "If one assumes that an absolutely low expectancy of goal attainment rather than just an independence of responses and outcomes is the key antecedent of depression, then hopelessness rather than helplessness would be the appropriate concept to emphasize". Hollon & Garber (1980) also agree about the centrality of hopelessness rather than helplessness in the aetiology of depression. They note that "negative expectations about the future produce much of the depressive symptomatology".

Beck's cognitive theory

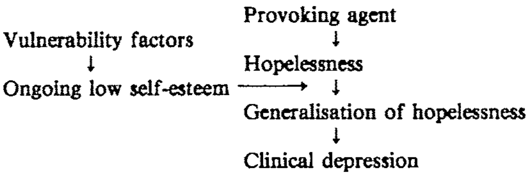
Beck's cognitive theory of depression, although first proposed in the 1960s, has retained its place as the cornerstone of the cognitive approach to depression in terms of both theory and therapy. Beck sees a negative view of the future as one of the elements of the 'cognitive triad', a set of negative attitudes to the world, the self, and the future, which is seen to be characteristic of the thinking of the depressive. He refers to this element of the triad variously as a negative viewpoint, negative expectations about the future, pessimism, or hopelessness (Beck *et al*, 1974*a*). By 1979, when *Cognitive Therapy of Depression* was published, the term 'hopelessness' is used almost exclusively (Beck *et al*, 1979). According to Beck & Rush (1978), the depressed patient "anticipates that his current difficulties or suffering will continue indefinitely. As he looks ahead he sees a life of unremitting hardship, frustration and deprivation".

In terms of the origins of a negative attitude towards the future, Beck does not offer a specific causal theory. He clearly sees the three elements of the cognitive triad as developing and functioning hand in hand, saying, for example, "Since the formation of the three types of concepts central to depression is similar we can use the development of self-concepts as a model for the other two" (Beck & Rush, 1978). He offers no evidence as to why the development of the three components should be similar. Beck *et al* (1985) come a little closer to a specific aetiological viewpoint concerning hopelessness. Episodes of hopelessness, they suggest, may reflect the activation of specific cognitive schemes organised in a matrix of negative expectations. When these negative schemes are activated by life experience, they tend to have a controlling effect on the nature of the patient's beliefs regarding the outcome of his/her immediate and future goals and well-being.

Although Beck would clearly expect that hopelessness is a more salient symptom in some depressed people than in others (he does, for example, suggest strategies for dealing with particularly hopeless clients (Beck *et al* 1979)), in the main body of his theory no room is given to the possibility that depression may exist without hopelessness (implying a cognitive dyad?) or vice versa. Beck *et al* (1985) stated, "Some individuals who become depressed display more hopelessness than do other individuals at the same level of depression", and "Patients with psychiatric disorders other than depression may show a consistently high level of hopelessness associated with each episode". However, in the same paper hopelessness is described as "a core characteristic of depression". Thus, from Beck's point of view "a negative view of the future is part of the triad of negative cognitions which produce the array of pathological changes typical of the depressive syndrome. Hopelessness is both a determinant and a component of the depressive condition."

Brown and Harris's model

In *Social Origins of Depression*, Brown & Harris (1978) aimed to develop a causal model of depression, the nature of their investigation being shaped by their assumption that "depression is an understandable response to adversity". Their complex model, developed on the basis of data collected from a random sample of women living in Camberwell and from a sample of psychiatric in- and out-patients, consists of vulnerability factors, symptom-formation factors, and provoking agents. In terms of the nature of provoking agents, they conclude that the common feature is loss. They continue, "The implications of loss usually stretch far beyond the fact of the loss itself. Like Melges & Bowlby we believe hopelessness is the key factor in the genesis of clinical depression and loss is probably the most likely cause of profound hopelessness". Loss usually triggers a sense of hopelessness, but in some cases it is generalised. They say, "It is such generalization of hopelessness that we believe forms the central core of a depressive disorder". It is a person's ongoing self-esteem which determines whether or not generalised hopelessness develops. The vulnerability factors already mentioned, which in the Brown & Harris (1978) sample included low socio-economic status, have their effect by bringing about low self-esteem in particular. Thus the theoretical model appears as follows:



In terms of symptom-formation factors, past loss by death is seen to lead to the retarded hopelessness of the psychotic and loss by separation to 'protesting despair'.

Depression, then, according to Brown & Harris (1978), "arises in a context of hopelessness, consequent upon the loss of important sources of reward or positive value". Although there have been many attempts to assess the validity of Brown and Harris's model, some reviews of their methodology and some replications of their findings (Tennant & Bebbington, 1978; Cochrane & Stopes-Roe, 1981; Tennant *et al*, 1981), neither they nor their critics seem to have questioned the role of hopelessness in the aetiology of depression.

Empirical evidence for the independence of hopelessness and depression

Brown & Harris's and Beck's theories have been very widely cited and, despite the fact that they are ignoring the complex and heterogeneous nature of depression, have been allowed to stand comparatively intact and unassailed. This is perhaps surprising when the amount of contradictory evidence that has accumulated in recent years is reviewed.

Some of the most substantial evidence for the functional independence of hopelessness and depression comes from the research on the relationship of each to suicidal intent. In a series of papers (Minkoff *et al*, 1973; Beck *et al*, 1975; Kovacs *et al*, 1975; Wetzel, 1976; Goldney, 1979; Wetzel *et al*, 1980; Petrie & Chamberlain, 1983; Kazdin *et al*, 1983; Dyer & Kreitman, 1984) suicidal intent was found to be more highly correlated with hopelessness than with depression, and this high correlation between hopelessness and suicidal intent was found to be maintained when the influence of depression was controlled. There are two studies which report contradictory findings, that of Pokorny *et al* (1975), and data in the Wetzel (1976) paper, which relate to 48 suicide attempters assessed by means of the Suicide Intent Scale (Beck *et al*, 1974*b*). However, the findings generally have been consistent, particularly when it is noted that they have been collected from different countries, i.e. the USA, Australia, New Zealand and Great Britain, and that the Kazdin *et al* (1983) paper involved children rather than adults.

Greene (1981) reported the Hopelessness Scale (HS) scores of a representative sample of 396 adults living in Dublin. The HS is a 20-item true/false scale consisting of statements such as "It is very unlikely I will get any real satisfaction in the future" and "I can look forward to more good times than bad times". The total possible score is 20 (Beck *et al*, 1974*b*). It is the most widely used measure of hopelessness. One feature of the pattern of HS scores is particularly relevant here. Measured hopelessness was not found to be related to the sex of the respondents (mean HS score for men, 4.12; for women 4.68; ±1.79, NS). However, if hopelessness is a necessary component of depression, it should be distributed in the same kind of pattern as depression, that is, with higher rates in females than in males (see Weissman & Klerman, 1977).

In a paper entitled "Hopelessness and depression", Nekanda-Trepka *et al* (1983) reported the results of two studies. In the first, 86 depressed people (mean Beck Depression Inventory (BDI) score $=27$, s.d. $=7.3$) had a mean HS score of 13.05 (s.d. $=5.17$). The HS scores were found to correlate with the BDI ($r=0.47$), but not with a variety of other variables and assessments (age, education, SES, duration of illness, severity of symptoms, sex, Hamilton Rating Scale for Depression). Eleven of the subjects obtained a score of less than 6 on the HS (i.e. within normal limits). In the second study, 20 subjects had a mean HS score of 11.1 (s.d. $=6.15$, range 0–20) and a mean BDI of 25.3 (s.d. $=6.2$). The BDI–HS correlation was $r=0.45$.

The authors point out that a number of their depressed subjects did not seem to be hopeless. They conclude that "If a negative view of the future . . . entails hopelessness it must be concluded that a negative view of the future is not universal in depressed patients". They also found support for the relationship between hopelessness and suicidal ideation, pointing out that "whilst not all depressed patients feel hopeless, the more hopeless are likely to have strong suicidal wishes". The authors do not spell out the implications of their findings any further than this.

The following two studies were carried out by the author consecutively, as part of a series of explorations of the correlates of hopelessness and its relationship to depression. For the purposes of these investigations the primary measure of hopelessness was the HS (Beck *et al*, 1974*b*).

Investigation 1

Method

Subjects. The 60 subjects (age range 18–65, mean 41, s.d. 13.6) comprised 40 psychiatric in-patients (20 men, 20

TABLE I

Correlations between BDI items and HS items, and between HS total score and BDI and HS items

BDI items	*BDI total score*	*HS total score*	*HS items*	*BDI total score*	*HS total score*
Sadness	0.72	0.73	1	0.47	0.68
Pessimism	0.70	0.75	2	0.54	0.30
Failure	0.77	0.55	3	0.42	0.54
Dissatisfaction	0.69	0.62	4	0.10*	0.09*
Guilt	0.73	0.53	5	0.37	0.45
Punishment	0.55	0.41	6	0.20*	0.56
Self-dislike	0.73	0.52	7	0.70	0.73
Self-blame	0.45	0.17*	8	0.13*	0.18*
Suicide	0.61	0.61	9	0.44	0.54
Crying	0.55	0.35	10	0.36	0.40
Irritability	0.39	0.14*	11	0.67	0.82
Withdrawal	0.49	0.36	12	0.55	0.64
Indecisiveness	0.59	0.50	13	0.30	0.68
Body image change	0.57	0.41	14	0.44	0.57
Work retardation	0.30	0.22	15	0.36	0.68
Insomnia	0.47	0.27	16	0.44	0.60
Fatigue	0.40	0.23	17	0.57	0.78
Anorexia	0.49	0.40	18	0.39	0.61
Weight loss	0.13*	-0.06*	19	0.20*	0.61
Somatic concerns	0.29	0.03*	20	0.44	0.68
Loss of libido	0.50	0.17*			

All significant at $P<0.05$ level, *except* where asterisked.

women) and 20 out-patients (10 men, 10 women) attending a psychiatric clinic. All subjects were diagnosed as clinically depressed by a psychiatric consultant.

Measures and procedure. As part of a larger study examining the effects of life stressors on levels of hopelessness in clinically depressed subjects, the BDI (Beck *et al*, 1961) and the HS (Beck *et al*, 1974*b*) were administered to all subjects. The BDI is widely used to assess the severity of depression.

Results

The mean BDI score for all 60 subjects was 26.8 (s.d. = 12.9, range 5.53). There was no difference between in-patients and out-patients. The mean HS score was 10.82 (s.d. = 5.42, range 1–10), considerably higher than the mean score of 4.45 (s.d. 0.69) for a normal population (Greene, 1981).

The correlation between HS and BDI scores was $r=0.69$ (Pearson's correlation coefficient, $P<0.001$). These findings in general are not dissimilar to those reported by Nekanda-Trepka *et al* (1983).

Discussion: Investigation 1

It should be noted that even a highly statistically significant correlation of 0.69 accounts for only approximately 50% of the total variance in responses to the two scales. Also, most importantly, among the subjects rated by their own psychiatrist as clinically depressed, the HS scores were uniformly distributed. A χ^2 goodness-of-fit test of the null hypothesis that the distribution was uniform did not allow rejection of this hypothesis ($\chi^2=4.33$, d.f. = 8, NS). This suggests that although the level of HS scores is high in this depressed group, hopelessness and depression are to a degree independent of each other, and the depressed person is as likely to be low as high in measured hopelessness. If the BDI were taken as the diagnostic index of depression, a purpose for which it was not intended, the position is rather different since, as indicated by the correation coefficient of 0.69, the individual who obtains a high BDI score is also likely to obtain a high HS score. There are, however, seven people who scored above 20 on the BDI and below 8 on the HS, and who would thus be considered as clinically depressed on the BDI and not hopeless on the HS (Greene, 1981).

It should be noted that the high correlation between BDI and HS scores may be due to the content overlap between the two scales. One way to examine this content overlap is to compute item-score–total-score correlations across and within the two tests (Table I). As would be expected from two tests purporting to measure different things, a large majority of the within-test item–total correlations are higher than the between-test item–total correlations. However, there is an amount of overlap, since very few of the between-test item–total correlations are non-significant statistically (at the $P<0.05$ level). The few cases where the BDI-item–HS-total correlation is higher than the BDI-item–BDI-total correlation are particularly interesting. Sadness and pessimism on the BDI correlate at a slightly higher level with the HS total score than with the BDI total score and at a high level (0.73 and 0.75). The same correlation is obtained between suicide and BDI total score and HS total score (0.61).

Pichot & Lempérière (1964) found that these items loaded heavily on the third factor of their four-factor solution to the BDI and labelled it depression–suicide. Furthermore, hopelessness as measured by the HS does not relate strongly to BDI items dealing with self-blame, irritability, loss of weight, somatic concerns, and loss of libido. Principal-component factor analysis with varimax rotation of BDI and HS item scores show a similar picture (Table II). The three-factor solution was selected since the factors were clearest. These results also show the existence of a 'hopelessness' component within the BDI. Factor 1 could be seen as the HS factor, since 15 HS items and only BDI items sadness, pessimism, suicidal intent and insomnia have loadings above 0.4 on this factor.

There would appear to be sufficient grounds to conclude that the HS and the BDI are not measuring the same phenomena. However, the BDI is much broader, and subsumes a measurement of hopelessness. This may account for much of the correlation between the BDI and the HS. It is unwise, however, to ignore the characteristics of the measures employed, and on finding a correlation between BDI and HS scores, go beyond the psychometric data to draw unjustified conclusions.

Aside from the fact that high BDI–HS correlations may be due to the shared territory between the measures, it is also possible that the BDI–HS correlation is due to response sets and/or styles among the subjects that cause them to respond differently from each other but similarly to both self-report measures. The minority of subjects who scored high on the BDI and low on the HS contradict this as a general explanation, but it may operate as a partial explanation for the majority of subjects. The second investigation was designed to avoid some of the problems arising from the confounding of BDI and HS scores by preselecting from a group of subjects with the same level of BDI scores, groups with high and low HS scores. Having selected two groups of highly depressed women with different levels of hopelessness, the aim was to examine characteristics

TABLE II

Principal-components factor analysis of BDI and HS items – three-factor solution

BDI items	*Factors*			*HS items*	*Factors*		
	1	*2*	*3*		*1*	*2*	*3*
Sadness	0.51	0.53	0.26	1	0.50	0.39	0.09
Pessimism	0.58	0.38	0.45	2	0.27	0.52	0.15
Failure	0.28	0.59	0.32	3	0.43	0.45	−0.15
Dissatisfaction	0.27	0.52	0.46	4	0.00	−0.04	0.19
Guilt	0.27	0.63	0.23	5	0.28	0.35	0.08
Punishment	0.23	0.21	0.39	6	0.58	−0.01	0.09
Self-dislike	0.26	0.71	0.14	7	0.50	0.33	0.59
Self-blame	0.06	0.24	0.15	8	0.04	0.23	−0.07
Suicide	0.47	0.48	0.17	9	0.42	0.37	0.10
Crying	0.15	0.39	0.18	10	0.13	0.37	0.12
Irritability	−0.06	0.24	0.19	11	0.61	0.31	0.52
Withdrawal	0.12	0.47	0.17	12	0.43	0.15	0.64
Indecisiveness	0.26	0.43	0.32	13	0.77	−0.02	0.04
Body image change	0.17	0.51	0.27	14	0.41	0.17	0.41
Work retardation	0.07	0.46	−0.18	15	0.67	0.08	0.12
Insomnia	0.60	0.40	0.26	16	0.48	0.34	0.06
Fatigue	−0.01	0.51	0.01	17	0.70	0.29	0.25
Anorexia	0.07	0.49	0.24	18	0.48	0.14	0.38
Weight loss	−0.25	0.02	0.20	19	0.71	0.02	−0.10
Somatic concerns	−0.07	0.13	0.39	20	0.65	0.25	0.09
Loss of libido	−0.07	0.59	−0.02				

of these two groups to see in what other ways, if any, they might be distinguishable from each other.

Investigation 2

Subjects and measures

Twenty women (age range 19–56) were selected, all of whom were psychiatric hospital in-patients with a primary diagnosis of depression. All but one were on antidepressant medication. Patients receiving ECT were excluded, as were subjects scoring below 20 on the BDI. After taking the HS, subjects were allocated to the high-HS group if their score was 11 or higher, and the low-HS group if their score was 8 or lower. These cut-off points were decided on the basis of their being less than 1 s.d. (3.09) above the mean (4.45) for the general population, or more than 2 s.d.s above the mean for the general population (Greene, 1981). The high-HS group had a mean HS score of 16 (s.d. 2.8), and the low-HS group had a mean score of 5.5 (s.d. 2.17). The final sample consisted of ten subjects in each group. Seventy-two women were assessed by means of the BDI and HS before both groups were complete, and the high scoring HS group was complete by the time the 37th person was seen.

Aside from the BDI and the HS, all subjects were given the following tests. (a) The Life Experiences Survey LES; (Sarason *et al*, 1978), a 47-item self-report inventory which identifies recent life events and allows the person to evaluate their impact on a seven-point scale, ranging from extremely positive to extremely negative. (b) The Cognitive Bias Questionnaire (CBQ; Krantz & Hammen, 1979), which measures cognitive stylistic distortions assumed to be typical of depressive thinking. This questionnaire consists of six stories, to which subjects are asked to respond by ticking the item in the attached sets of statements that represents their likely feelings and responses, had they been the protagonists in the story. The four items in each set of statements represent a depressed/distorted response, a non-depressed/distorted response, a depressed/non-distorted response, and a non-depressed/non-distorted response. Most of the 23 sets of responses refer to present time; four refer to the future. In order to test the hypothesis that subjects who are higher in measured hopelessness show higher levels of cognitive distortion in relation to the future, the four future-orientated sets of responses to stories B, C, E and F were used, with the addition of a new set of future-orientated statements to story A. Thus if a subject produces five depressed/distorted responses on these particular sets, her depressed/distorted future-orientated (FO) score is 5. If she produces none, her score is 0. (c) The Rosenberg Self-Esteem Scale (Rosenberg, 1965), a widely used ten-item scale for assessing self-esteem. (d) The Experiential Inventory, a method of tapping time orientation developed by Cottle (1968). It is scored in terms of past, present, or future orientation. (e) Subjects were also given an open-ended questionnaire on their attitudes to their circumstances and future. This questionnaire was designed to supplement the HS, which, being of a standard true/false format, does not give much scope for individuality of response. Demographic information was collected in a questionnaire covering family background, education, work, housing, and history of mental and physical health.

Results

It is significant in itself that it was possible to find a sample of very depressed women who were low on measured hopelessness. In the 72 in-patient women with a primary diagnosis of depression who were screened, the pattern of high depression/high hopelessness was approximately three times more common than high depression/low hopelessness. (Approximately half the women screened obtained BDI scores under 20 and were thus classified as 'low depression' according to the criterion being employed here.)

The next step was to find out whether the difference in hopelessness was extended to other differences in a meaningful way. A pattern of similarities and differences emerged between the two groups (Table III). The similarities are noted first.

(a) There was no significant difference in BDI scores: according to Beck's categorisation system, both groups are, on average, severely depressed (Beck, 1967).

(b) On the CBQ, both groups produced scores claimed to be typical of depressed subjects (Kranz & Hammen, 1979; Blaney *et al*, 1980). The high-HS group had a higher depressed/distorted score, but the difference between groups did not reach statistical significance.

(c) Both groups showed very low levels of self-esteem with scores for the high-HS group indicating lower self-esteem, but the differences between the groups' scores just failed to reach statistical significance ($t = 1.80$, $P < 0.1$).

(d) On the Experiential Inventory all subjects were past-orientated, and eight out of ten of both groups were classifiable as future-avoiders.

(e) On the LES, it can be seen that both groups have almost identical scores on the negative change index. Female subjects assessed by Sarason *et al* (1978) in their paper introducing the LES had a mean negative life change score of 7.04 (s.d. 7.90).

(f) Answers to the open-ended questions "Can you tell me what you are looking forward to today?", "Do you find it easy to picture the future?", "Do you avoid thinking about the future?", and "Do you worry about the future?" were very similar across the groups. Almost all subjects found it difficult to picture the future and did not think about it. Members of both groups reported many worries. As an illustration, answers are given below to the question, "Do you avoid thinking about the future?"

High-HS scores

"I avoid it because I find it difficult."

"I try to think about it but there isn't anything I can do. It'll all happen again. I think about the past often. I don't do it deliberately; it just comes. I try to stop thinking about it."

"I'm afraid I might do something if I think about it."

"Exactly. Yes."

"No, I'm always thinking about the future, in a very pessimistic way."

TABLE III

Comparison of test scores obtained by high-HS and low-HS groups

Measures	*High-HS group* (n = *10*) *Mean*	*s.d.*	*Low-HS group* (n = *10*) *Mean*	*s.d.*	t	*Significance level*
Hopelessness Scale	16	2.8	5.5	2.17	9.30	$P<0.001$
Beck Depression Inventory	31.7	7.1	27.5	9.5	1.11	NS
Cognitive Bias Questionnaire						
depressed/distorted	7.3	5.80	4.1	3.30	1.50	NS ($P<0.1$)
depressed/non-distorted	7.3	4.27	7.9	3.78	0.33	NS
non-depressed/distorted	2.0	1.82	2.7	1.94	0.82	NS
non-depressed/non-distorted	7.4	6.13	9.3	5.03	0.75	NS
depressed/distorted FO	2.2	1.45	0.6	1.10	2.77	$P<0.05$
depressed/non-distorted FO	1.6	0.96	2.1	0.73	1.13	NS
non-depressed/distorted FO	0.6	0.84	0.9	1.10	0.68	NS
non-depressed/non-distorted FO	0.6	1.00	1.4	1.20	1.38	NS
Rosenberg Self-Esteem Scale	2.9	1.80	4.7	2.50	1.80	NS ($P<0.1$)
Life Experiences Survey						
positive change	1.40	1.90	3.50	3.0	1.80	NS ($P<0.1$)
negative change	12.0	7.0	12.2	7.80	0.06	NS

"I avoid it. When I think of the future it's a complete blank."
"I've avoided thinking about it for the last few days."
"I don't see one. Not at the moment."
"I can't picture the future."
"I think about the past and avoid the future. I'd like to feel better and think about the future."

Low-HS scores
"I look forward to it. Seeing the children grow up. Seeing their satisfaction. Seeing them achieve something."
"I think about the past. My childhood memories are so happy. I've very dear memories of those things."
"I tend to avoid thinking about the future and I try not to dwell on the past."
"No, I don't avoid it. I think the future will bring good things, hopefully."
"I don't really think of the future. My husband would think of the future alright. I'm no good for projecting myself into the future really. It might be just my mood at the moment but I don't think I was able to look into the future ever."
"Well, tomorrow's another day. Something could happen tomorrow that you wouldn't want to happen."
"I think more about the past."
"I think more about now. I don't want to die. When the depression gets on top of me, I think I'm in everybody's way."
"I hope I'll be able to cope better in the future. I always got over my depression before."
"I have faith in the future but I don't want to think about it. It may not be good but I'll be able to withstand it."

In terms of differences between the groups, the following results were found.

(a) The high-HS group produced significantly more depressed/distorted responses to future-orientated material than did the low-HS group.
(b) The positive change on the LES is higher for the low-HS group, although the difference between the groups just fails to reach statistical significance.
(c) In terms of demographic characteristics, the only difference which emerged as statistically significant was that concerning the presence or absence of young children (Fisher's exact test, $P=0.005$). There were no women in the high-HS group who had children under the age of ten, although two had grown-up children, whereas six women in the low-HS group had young children. There were more married women in the low-HS group, but the difference between the groups in terms of marital status failed to reach statistical significance.
(d) In answer to the open-ended question "What are you looking forward to in the next few weeks?", five of the high-HS group mentioned positive events in the future, whereas all ten of the low-HS group did so. Five of the women of the high-HS group mentioned "getting out of here" or "going home" as events they looked forward to, which contrasted with the specific emphasis, almost amounting to expectation, which was placed on getting better by five of the low-HS group.

In answer to the question "What are you looking forward to in the next few years?", five of the high-HS group mentioned positive events, and nine of the low-HS group were unequivocally positive about the future, and one was neutral. None of this group expressed negative expectations, unlike some of the high-HS group who mixed positive with negative expectations. The low-HS group tended to bring their children into their anticipations for the future, and felt very concerned about seeing them grow up happily. Three of the four single women in the low-HS group who had no children mentioned their desire to have children in the future. (The remaining woman was 47 years old.)

Discussion: Investigation 2

To recapitulate, on screening it was found that approximately one in four psychiatric in-patient women diagnosed as depressed and scoring above 20 on the BDI had the high-depression/low-hopelessness pattern. It would seem then, on the basis of both investigations 1 and 2, that people can be found who are definitely depressed in all normal senses of the word but who do not show signs of hopelessness. Furthermore, comparison of severely depressed women who are high on measured hopelessness with those who are low on measured hopelessness reveals a meaningful pattern of similarities and differences. Both groups have many of the characteristics to be expected of women who are severely depressed, but the low-hopelessness group is more likely to have young children and to have had more positive life events in the recent past. It is possible that positive life experiences and being the mother of young children together function as a protection against the development of hopelessness. The possible process by which being involved in mothering young children protects women against hopelessness clearly does not function to protect them against depression *per se*, as many studies would testify (Richman, 1976; Moss & Plewis, 1977; Brown & Harris, 1978). In this study, negative life events have not been found to correlate with HS scores specifically, and it may well be that the quest for factors that protect against hopelessness might be more fruitful than the quest for social or environmental stressors that contribute towards it.

Several of the findings serve mainly to validate the HS as a measure of hopelessness, in that the subjects' responses to the future were found to be different in important ways. In terms of present-orientated cognitive distortion, the groups are broadly similar, and they both avoid thinking about the future. By definition, the hopeless depressives have more negative expectancies about the future. They also show evidence of cognitive distortion *vis à vis* future events. However, the hopeless depressive in this sample does not typically brood about the goals she is unlikely to achieve or the awful events that may befall her. When forced to verbalise their thoughts about the future, the hopeless patients appeared to find difficulty in describing their futures except in terms of blankness or darkness, very gloomy but non-precise terms. The low-HS patients have equally imprecise, but vaguely benevolent views of their futures.

General discussion

Beck & Rush (1978) described hopelessness in terms of the projection of current negative cognitions into the future, saying "as the person makes long range projections, he anticipates that his current difficulties or suffering will continue indefinitely". It seems more likely that the person who is prone to hopelessness has a cognitive set specific to the future which dictates that the future holds no possibility of good or fulfilment. This set is stimulated whenever the person is forced to think about his/her future, and the aversive response the person experiences in reaction to it is accompanied by the affective and motivational disturbances typical of the hopeless state. The non-hopeless person, even the depressed non-hopeless person, has, on the other hand, a positive cognitive set towards the future, despite the miseries experienced in the present.

There are many possible origins of hopelessness. For example, a lack of faith in the future may be engendered in infancy by a failure to develop trust. Erikson (1950) argued that trust is the foundation of a healthy personality. It is possible that contemporaneous factors may over-ride a basically mistrustful and pessimistic cognitive set, if they are sufficiently powerful. Thus, in some people, having young children may generate the kind of considerations that can cancel out the hopelessness. On the other hand, it is possible that some people develop a non-specific faith or hope in the future which is so basic that it is strong enough to coexist with a disabling and distressing level of depression.

Conclusion

Given the established connection between hopelessness and suicide, there is a pressing need to understand its origins and determinants. The findings reported here suggest that it might be more fruitful to ask why some people lack hope rather than why they 'have' hopelessness.

It is possible to review the state of current evidence and draw the important conclusion that hopelessness is neither an inevitable correlate nor an inevitable component of depression. A longitudinal investigation might possibly reveal a hopeless phase in the development of all depressions, but it is hard to envisage the mechanism by which such a powerful determinant could disappear completely at the height of the person's depressive disorder. This is not to deny the importance of establishing the aetiological role of hopelessness in those depressions (the majority) where it is salient.

It must be noted that samples studied here are small and possibly not representative of all clinically depressed people. Nonetheless, the suggestion can be made that there are two distinguishable types of depressive, the hopeless and the non-hopeless. This statement requires further confirmation; nevertheless, in formal aetiological theories of depression, whether psychological or biological, the heterogeneity of depression is rarely recognised. At the most, the reactive–endogenous distinction may be accepted, and theorists may confine their speculations to one or other of these types.

It might be argued that simplistic unitary theories have served their undoubtedly useful heuristic purpose, and it is now time to take a more complete account of the multifaceted and varied manifestations of clinical depression. One way of doing this is to look more closely at the assumed components of the depressive condition, such as guilt, low self-esteem, loss of appetite, etc. Hopelessness serves as but one example, but a particularly relevant one, of a condition which is assumed to be an essential feature of depression but in fact is not. If non-hopeless depressives exist, as the investigations reported here strongly suggest, then it is no longer acceptable to see hopelessness as "the key factor in the genesis of clinical depression" (Brown & Harris, 1978).

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The Hormonal Environment of Post-natal Depression

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The incidence of post-natal depression is high, and dramatic changes in steroid hormones and prolactin occur in the post-partum period. In an attempt to correlate these events, 147 mothers, six to eight weeks after delivery of a healthy infant, completed standard psychological tests, including the Edinburgh, Montgomery–Åsberg, and Raskin scales. They also provided matched samples of plasma for assay of cortisol, oestradiol, progesterone and prolactin, and saliva for assay of cortisol and progesterone. All steroid concentrations were within the appropriate normal ranges. Of the mothers, 14.9% were depressed on all three scales. Significant correlations were seen between depression ratings and salivary progesterone and prolactin. In bottle-feeders, salivary progesterone was positively associated with depression, whereas in breast-feeders it was negatively associated. Plasma prolactin levels were inappropriately low in depressed breast-feeders. These data indicate that differing therapies may be appropriate for depression in breast- and bottle-feeders.

All the major population studies of mothers during the year after delivery report a high incidence of post-natal depression. In approximately 300 mothers followed through into the late puerperium after delivery at the London Hospital, the incidence of post-natal depression was 10.8% (Pitt, 1968). Similarly, in a group of 120 mothers screened for depression while attending a routine post-natal clinic six weeks after delivery, Paykel *et al* (1980) found symptoms of mild depression in 20%. The Edinburgh Postnatal Depression Scale (Cox *et al*, 1987) was introduced partly as a screening procedure to aid identification of such patients.

Factors found to be associated with this condition include an increased number of life events during the preceding 12 months, previous psychiatric illness (Paykel *et al*, 1980), marital disharmony (Kumar & Robson, 1984; Watson *et al*, 1984), and a higher level of neurotic symptoms when well (Cox *et al*, 1982).

'Post-partum blues' refers to the minor depressive symptoms which may become more pronounced four days after delivery (Cox *et al*, 1982). This distinctly time-associated phenomenon, which in the study of Paykel *et al* (1980) had an association with subsequent post-natal depression only in the absence of life events, may have an underlying hormonal basis. Certainly, after delivery, major changes occur in circulating concentrations of numerous hormones, including progesterone, oestradiol, cortisol, prolactin, and possibly endorphins. It is conceivable that there may be an association between the fall of progesterone concentrations after delivery and the subsequent onset of depression and anxious mood. Indeed, progesterone therapy has been advocated as a treatment for post-natal depression (Dalton, 1983); but before advocating prophylactic supplementation, it is essential to demonstrate unequivocally that women with post-natal depression have a progesterone deficit. Comparison of progesterone levels in depressed and non-depressed mothers was therefore a major objective of this study.

Attempts to monitor changes in hormone levels before and after delivery have relied almost exclusively on measurement of plasma steroids. Thus the total (protein-bound plus free) progesterone and oestradiol concentrations have been reported (Nott *et al*, 1976) rather than the free, biologically active component of the hormone. When circulating in the blood, progesterone is extensively bound to cortisol-binding globulin (CBG), while oestradiol is bound by sex-hormone-binding globulin (SHBG). Anderson *et al* (1985) have shown that, although total hormone concentrations are greatly increased at the end of pregnancy, plasma 'free' values remain relatively low (progesterone 1.76–2.77%, oestradiol 0.84–2.7%). It is the ratio of free oestradiol to free progesterone that is important as a predictor of labour (Darne *et al*, 1987). Since data relating to changes in 'free' hormone concentrations are sparse, the possibility remains that changes in 'free' biologically active hormone(s) may be of importance in modulating mood.

Saliva is a useful alternative to plasma for the analysis of progesterone and cortisol, particularly since the development of sensitive radioimmunoassays (RIAs), which facilitate precise determination of the low levels of these steroids. It has also been demonstrated that salivary concentrations of most neutral steroids reflect plasma 'free' levels (Riad-Fahmy *et al*, 1982), and that saliva concentrations reflect those in plasma regardless of the salivary flow rate (Cook *et al*, 1986). In addition, saliva samples are easily collected without causing stress, at home, and thus multiple samples may be obtained in conjunction with assessment of mood (Feksi *et al*, 1984). It appeared worthwhile therefore, to increase the understanding of the possible modulating influence of steroids in post-natal depression by measuring salivary hormone concentrations at a time when some women were depressed, and to compare such data with those derived from a non-depressed group.

Methods

Subjects

Over the course of a year (1984–85), 147 mothers were assessed at the Caerphilly District Miners' Hospital, South Wales. The mothers had all had routine bookings for delivery at the hospital: the mean length of gestation was 16 weeks at presentation. The age range of the subjects was 17–40 years (mean 24.6), and parity varied from one to five, with 98 mothers having had children previously. Psychiatric assessment of the mothers was at a routine post-natal follow-up clinic, approximately six to eight weeks after delivery.

The women participating in this study were part of a larger investigation of the role of post-partum thyroid dysfunction (Fung *et al*, 1988). Sixty-five mothers were found to be antibody positive (microsomal and antithyroglobulin), and the remainder were antibody negative. They were otherwise medically unscreened. Application of Pearson correlation matrices to this database failed to demonstrate any association between thyroid-antibody status and non-thyroidal hormone parameters. Of the 147 mothers participating, 138 had vaginal deliveries, and nine had Caesarean sections: no mothers delivered either a stillborn or severely handicapped baby.

Mode of feeding

At the time of assessment, 29 women stated that they were breast-feeding their babies, whereas 118 were bottle-feeding. In breast-feeders, detailed information regarding the relationship between feeding and sampling time was not requested, since measurement of prolactin, the only hormone known to show gross changes after feeding, was not originally envisaged.

Psychiatric assessments

Each mother was assessed clinically in the afternoon (13.30–15.00 h) by one experienced psychiatrist (BH). The following questionnaires were also used: the Edinburgh Postnatal Depression Scale (Cox *et al*, 1987), the Raskin 3 Area Scale for Depression (Raskin *et al*, 1970), the Montgomery–Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), and the Beck Depression Inventory (Beck *et al*, 1961); with cut-off scores of greater than 12 for the Edinburgh scale, greater than 7 for the Raskin scale (Paykel *et al*, 1980), and greater than 11 for the Montgomery–Åsberg scale. A study by Snaith *et al* (1986) indicated that mild depression on the Montgomery–Åsberg scale scored between 7 and 18 (inclusive): thus the cut-off point in the present study represents the mid-point of this range. No cut-off point was used for the Beck Depression Inventory, since it was included only to examine correlations with other scales.

Sample collection

At the time of psychiatric assessment, six to eight weeks after delivery, a matched blood and saliva sample was collected from each subject. In addition, each mother was provided with a set of plastic tubes (5 ml Z/5, Steralin Ltd, Feltham, England) to be used for collection of a saliva sample at 22.00 h that evening and again at 08.00 h the following morning. These two saliva samples, collected at home, were returned by mail to the laboratory. All samples (plasma and saliva) were stored at −20°C within an hour of receipt. Each mother was sent £2 on receipt of saliva samples and completed questionnaires. To assess the effect of delays in the postal system on steroid concentrations, 20 additional samples of saliva were collected from mothers at 14.00 h. Each sample was divided into two, one half being sent through the post by first-class mail, the other half being deep-frozen within an hour of collection. The matched samples of saliva were subsequently analysed within the same assay, and no significant differences were found for either progesterone or cortisol concentrations.

Hormone analyses

Plasma progesterone and oestradiol concentrations were determined by direct RIAs using kits supplied by Diagnostic Products Ltd and Steranti Ltd, respectively. However, since plasma progesterone concentrations proved to be at or below the sensitivity of the kit, samples were re-assayed by the more sensitive procedure used for measurement of this steroid in saliva. Measurement of plasma cortisol relied on a direct 'in-house' RIA (Riad-Fahmy *et al*, 1979). Plasma prolactin concentrations were determined at the Supra Regional Assay Service Protein Hormone Laboratory, University of Wales College of Medicine, Cardiff, using an 'in-house' assay.

Salivary progesterone and cortisol were determined using the previously reported procedures of Walker *et al* (1978, 1979).

Statistical analyses

The data were analysed using the Pearson correlation matrix, and a series of Student's *t*-tests. Since the hormone data showed a skew distribution, logarithmic transformation of the hormonal concentrations was performed, which resulted in a more normal distribution. Correlations between various parameters were based on slightly differing numbers of subjects, owing to varying rates of compliance.

Results

All plasma and salivary hormone concentrations were within normal physiological ranges.

Compliance

Of the 147 women contacted initially at antenatal clinic, 49 failed to keep their post-natal appointment. These women were therefore visited at home, and assessed during the afternoon at approximately the same time as they would have been at the post-natal appointment clinic. Only 20 mothers did not return their saliva samples and home questionnaires, while one other could not be contacted as she had left the area.

Relationship between plasma and salivary steroid concentrations

Matched plasma and saliva samples were provided by 132 subjects at approximately 15.00 h. Using the Pearson correlation matrix, cortisol concentrations were significantly related ($P<0.001$, $r=0.50$) as were progesterone concentrations ($P<0.001$, $r=0.451$).

The correlation of psychometric indices

As might be expected, the correlations between the Edinburgh, Raskin, and Montgomery–Åsberg scales were all found to be highly significant: Edinburgh/Raskin ($r=0.80$, $P<0.001$), Raskin/Montgomery–Åsberg ($r=0.92$, $P<0.001$). The Beck scale correlated well with other scales, but the associations were weaker: Beck/Edinburgh ($r=0.68$, $P<0.001$), Beck/Raskin ($r=0.62$, $P<0.001$), and Beck/Montgomery–Åsberg ($r=0.61$, $P<0.001$).

Categorisation based on cut-off points for psychometric indices

Analysis of the questionnaires showed that 14.9% of patients were depressed on the three questionnaires, an additional 4.9% were depressed on two questionnaires, and a further 9% had depressive symptoms on one questionnaire only. For individual questionnaires the rates were: Edinburgh 22%; Raskin 25%; Montgomery–Åsberg 17%. Moreover, the rates of depression in breast- and bottle-feeders were similar (e.g. Edinburgh scale: 19% and 23% respectively).

There were no discrepancies in the categorisation of patients; those scoring above the cut-off point on all three questionnaires were all judged to be depressed on clinical assessment.

Hormonal v. psychometric indices

Data derived by measurement of plasma and salivary hormones in the various subgroups of depressed and non-depressed women are summarised in Table I. It is apparent that although hypercortisolaemia has been implicated in depression, this study revealed no consistent differences in either plasma or salivary cortisol concentrations between depressed and non-depressed women. Plasma oestradiol concentrations also showed no consistent differences between depressed and non-depressed women. The higher concentrations of this steroid in bottle-feeding women not taking a contraceptive pill are explicable in terms of their earlier resumption of follicular maturation. In marked contrast to cortisol and oestradiol, progesterone and prolactin concentrations were associated with differences in mood. These associations are detailed in Tables II and III respectively.

Salivary progesterone

The application of a series of Student's *t*-tests to the salivary progesterone data revealed no consistent differences between the mean concentrations in depressed and non-depressed women. Salivary progesterone concentrations at the three sampling times were most frequently associated on a Pearson correlation matrix with Beck scores. Data presented in Table II indicate that in bottle-feeders there was a positive association of progesterone with depressive symptoms: the reverse was true for breast-feeders.

Plasma prolactin

In the total population, depression was significantly associated with decreased prolactin concentrations (Table III). In the non-depressed subgroups, the finding of consistently higher prolactin levels in breast-feeders is in keeping with consensus views on the stimulus of suckling. The significantly lower prolactin concentrations in the majority of subgroups of depressed women is noteworthy.

Discussion

It is reasonable to hypothesise that post-partum mood changes are linked to the changing concentrations of steroid hormones such as progesterone, oestradiol and cortisol, and possibly to variation in prolactin levels. Cortisol concentrations rise during pregnancy and, after delivery, there is a dramatic fall. There is approximately a 100-fold fall in plasma progesterone in the few days after delivery and a tenfold fall in oestradiol in the 24 hours after delivery (Butler & Leonard, 1986). As the menstrual cycle becomes re-established, there is firstly an increase in oestradiol, and then a later increase in progesterone. Prolactin levels rise during pregnancy, rise further after delivery, and thereafter levels are dependent on the mode of feeding, remaining high where breast-feeding is established.

TABLE I

Hormonal parameters in samples collected at 1500 h by post-partum women

	On contraceptive pill								*Not on contraceptive pill*							
	Depressed[1]				*Non-depressed*				*Depressed*[1]				*Non-depressed*			
	Mean[2]	*+s.d.*	*−s.d.*	n	*Mean*[2]	*+s.d.*	*−s.d.*	n	*Mean*[2]	*+s.d.*	*−s.d.*	n	*Mean*[2]	+s.d.	−s.d.	n
Bottle-feeders																
Plasma cortisol: nmol/l	357	531	240	6	236	402	139	18	150	249	90.5	9	192	359	103	70
Saliva cortisol: nmol/l	6.83	14.2	3.27	7	5.32	9.98	2.84	22	3.00	6.83	1.32	10	6.09	11.8	3.15	73
Plasma progesterone: nmol/l	0.923	5:11	0.167	7	0.356	0.750	0.169	20	1.23	7.32	0.21	9	0.94	3.75	0.23	71
Saliva progesterone: pmol/l	95.2	378	24.0	7	57.1	132	24.7	22	123	358	42.2	10	88.5	210	37.2	71
Plasma oestradiol: pmol/l	37.2	86.7	15.9	7	46.7	98.9	22.1	20	199	684	58	10	210	502	88	71
Breast-feeders																
Plasma cortisol: nmol/l	—	—	—	0	159	303	83.5	11	129	304	54.7	3	225	394	128	14
Saliva cortisol: nmol/l	—	—	—	0	5.51	8.01	3.79	11	6.49	8.41	5.00	3	5.72	15.5	2.11	14
Plasma progesterone: nmol/l	—	—	—	0	0.484	1.04	0.226	11	0.329	0.601	0.180	3	0.538	1.33	0.218	14
Saliva progesterone: pmol/l	—	—	—	0	79.4	300	21.0	10	55.4	139	22.2	2	82.8	239	28.7	13
Plasma oestradiol: pmol/l	—	—	—	0	58.4	114	29.9	11	84.3	175	44.1	3	75.6	138	41.3	14

1. Depressed = women scoring above cut-off points on Edinburgh, Raskin *or* Montgomery–Åsberg scales.
2. Geometric mean.

TABLE II

Psychometric variables significantly associated with salivary progesterone concentrations (pmol/l) in samples collected at stated times

Population	*Time*	*Depression variable*	n	r *value*[1]	*Significance* (P)
Overall	08.00	Beck	126	0.24	0.05
Bottle-feeders (all)	08.00	Beck	99	0.36	0.001
	15.00	Beck	96	0.31	0.002
	22.00	Beck	99	0.22	0.05
Bottle-feeders (−pill)	08.00	Beck	72	0.28	0.05
Bottle-feeders (+pill)	08.00	Beck	26	0.56	0.003
		Edinburgh	20	0.45	0.04
		Raskin	27	0.48	0.01
		Montgomery–Åsberg	27	0.55	0.003
	15.00	Beck	26	0.46	0.02
Breast-feeders (all)	08.00	Edinburgh	25	−0.40	0.05
	15.00	Beck	26	−0.54	0.01
	22.00	Edinburgh	25	−0.44	0.05
	22.00	Raskin	27	−0.41	0.05
	22.00	Montgomery–Åsberg	27	−0.57	0.01
	22.00	Beck	27	−0.57	0.01
Breast-feeders (−pill)	15.00	Beck	16	−0.63	0.01
	22.00	Edinburgh	15	−0.65	0.01
	22.00	Raskin	17	−0.55	0.05
	22.00	Montgomery–Åsberg	17	−0.68	0.01
	22.00	Beck	17	−0.66	0.01
Breast-feeders (+pill)	08.00	Raskin	10	−0.65	0.05
	08.00	Montgomery–Åsberg	10	−0.74	0.05
	15.00	Montgomery–Åsberg	10	−0.64	0.05

[1] Correlation coefficients were calculated for all psychometric variables v. salivary progesterone at all sampling times. Only correlations significant at $P<0.05$ are shown.

Evidence implicating steroid hormones in behavioural change comes from a number of sources. Animal studies have shown that progesterone has an anxiolytic action in the oestrogen-primed female rat, but not in the androgenised or eunuchoid rat (Rodriguez-Sierra *et al*, 1986). Again, oestrogens in the ovariectomised rat can produce lordosis behaviour, and the rate at which this behaviour is produced can be varied by administration of progesterone (McEwen & Parsons, 1982). These changes in behaviour with changing steroid concentrations are thought to be linked to the central nervous system (CNS) via the hypothalamus (McEwan & Pfaff, 1985).

At the cellular level, oestrogens and progesterone are related to receptor levels on the surfaces of lymphocytes and platelets. The number of lymphocyte α-adrenoreceptors falls after childbirth, corresponding to a fall in the circulating levels of oestrogen and progesterone (Metz *et al*, 1983). Although of interest, peripheral models need not necessarily reflect events in the CNS. In rabbits, oestrogen treatment caused a significant decrease in α-adrenoreceptor number and function in platelets, but not in brain preparations (Mishra *et al*, 1985). In addition, Biegon *et al* (1983) report that, in the ovariectomised female rat, oestrogen induces a reduction in $5HT_1$ receptors and β-adrenergic receptors, with a concomitant increase in $5HT_2$ receptors. By contrast, progesterone alone increased $5HT_2$ and decreased $5HT_1$ receptors, but was without significant effect on noradrenergic receptors. When given with oestrogen, progesterone blocked the oestrogen-mediated increase in $5HT_2$ receptors, but did not inhibit the decrease in $5HT_1$ receptors or in β-adrenergic receptors.

Biegon *et al* (1983) emphasise that β-adrenergic and $5HT_2$ receptors are implicated in antidepressant action. Thus the modulation of these two receptor

TABLE III
Prolactin concentrations (mU/l) in samples collected at 15.00 h by post-partum women

Population	*Depressed*				*Non-depressed*				P[1]
	Mean	*+s.d.*	*−s.d.*	n	*Mean*	*+s.d.*	*−s.d.*	n	
Overall	232	387	139	32	337	787	145	64	0.008
Bottle-feeders (all)	208	321	135	26	246	410	148	52	NS
Breast-feeders (all)	373	675	206	6	1322	2483	704	12	0.002
Bottle-feeders (+pill)	256	394	166	7	205	348	121	10	NS
Bottle-feeders (−pill)	189	290	124	18	257	425	156	42	0.021
Breast-feeders (−pill)	254	376	172	3	1524	3234	718	7	0.002

[1] Significance of the differences between polactin concentrations in the depressed and non-depressed subgroups.

types by steroid hormones might be relevant to hormone-linked affective changes in the pre-menstrual and post-partum periods. Data from clinical studies indicating the importance of steroid hormones in affective disorders are, as yet, limited. In an open study, Dalton (1983) claims to have reduced the incidence of post-natal depression by giving daily prophylactic progesterone immediately after delivery for two months or until menstruation returned. Oestrogen has also been used, with some success, for treating persistently depressed women, in double-blind trials with placebo (Klaiber *et al*, 1979). These authors produced evidence that oestrogen therapy is related in such cases to mono-amine oxidase activity.

Despite these clinical findings, studies that have assessed steroid levels in the context of post-natal depression have failed to provide major findings. In an early study, Handley *et al* (1980) showed a minor association of puerperally depressed mood with high cortisol at 38 weeks' gestation. However, the same group later found no association between post-natal depression and plasma cortisol, oestrogen, or progesterone levels (Gard *et al*, 1986). Similarly, Nott *et al* (1976) found no association of mood in late pregnancy or the puerperium with plasma oestrogen and progesterone levels. More recently, Butler & Leonard (1986) found no association of plasma progesterone, oestradiol, or cortisol with depressed mood six to eight weeks post-partum.

By contrast, it is known that hypersecretion of cortisol is associated with 'endogenous types' of depression (Carroll *et al*, 1981). It has been hypothesised (Railton, 1961) that withdrawal of cortisol follows delivery, and that this drop in cortisol is a factor in producing post-natal depression. Railton has, in fact, administered prednisolone, and claims to have successfully treated post-natal depression. The present study provided no evidence for an association between plasma cortisol and depression. The only obvious finding was an elevation in plasma cortisol levels in bottle-feeders on the pill compared with those not taking contraceptive preparations. This is in accordance with the induced synthesis of CBG by synthetic oestrogens (Durber & Daly, 1976). Similar differences were neither found nor expected in breast-feeders, since this group would probably be taking a progestin-only preparation.

During the puerperium, major changes occur in circulating concentrations of binding proteins modulated both by changes in endogenous oestradiol, and by administered oestrogen-containing contraceptive preparations. Since the plasma 'free' steroids are generally accepted to be the biologically active moiety, measurement of this fraction is desirable but technically difficult. Salivary-based studies obviate these difficulties. The differing concentrations of binding proteins in puerperal subjects are reflected in the reduction in the coefficient (r) seen in correlations between salivary and plasma concentrations of the steroids, progesterone and cortisol. Thus, in the present study, the r values for both steroids were approximately 0.5 compared with r values >0.9 observed in studies of non-puerperal subjects (Walker *et al*, 1979; Vining *et al*, 1983).

Although saliva samples were collected at three time points, no consistent differences in salivary cortisol were seen between depressed and non-depressed subjects in any subgroup at any time point; thus only data derived from 15.00 h samples are shown in Table I. Data relating to salivary progesterone are of rather greater interest. In bottle-feeders, salivary progesterone at each time point correlated positively with several indices of depression, whereas in breast-feeders, salivary progesterone correlated negatively with such indices. These data therefore serve to emphasise the need for a clear distinction to be made in the treatment regimes advocated for women who breast-feed and those who bottle-feed. A deficit of progesterone is suggested in the depressed breast-feeding mothers. This appears to be confirmed by the lower incidence of depression in breast-feeders who take contraceptive preparations and, therefore, receive progestins. Thus there would appear to be some basis for advocating additional progesterone as a prophylactic measure against post-partum depression in breast-feeders. In the group of bottle-feeders, the converse holds true: depression is correlated positively with salivary progesterone. Furthermore, the incidence of depression in bottle-feeders taking the pill (24%), and thus receiving additional progestin, is higher than that in bottle-feeders not taking the pill (12%). These data militate against administering progesterone supplements in bottle-feeders.

These differing associations of progesterone and depression ratings in the two feeding groups prompted retrospective analysis of prolactin levels (Table III). There was also a significant difference in prolactin levels between the breast-feeders who were and were not depressed. In effect, concentrations of prolactin in depressed breast-feeders were at levels more appropriate for bottle-feeders. In breast-feeders there was a negative association between prolactin and depression ratings, but the association achieved significance only for the Edinburgh scale ($r = -0.66$; $P = 0.003$). While it is appreciated that the numbers of depressed breast-feeders are small, and that sampling time in this retrospective study was not controlled with regard to the last breast-feed, the much lower absolute concentrations of prolactin in the depressed mothers suggests it would be worthwhile to confirm these findings in a larger prospective study.

Lack of knowledge regarding the aetiology of post-natal depression makes rational prophalaxis or treatment difficult. Since this condition, like those of post-partum blues and pre-menstrual tension, occurs at times when circulating steroid concentrations are rapidly changing, frequent sampling is required to facilitate understanding of the complex aetiology of these conditions. Salivary-based investigations coupled with the use of simple psychiatric scores appear well suited for resolving such current psychiatric problems.

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Depression Following Spinal Cord Injury

A Prospective In-patient Study

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In a systematic prospective study of 71 patients with acute spinal cord injury carried out in the acute and rehabilitation phases of treatment, 14 patients meeting the DSM–III criteria for major depressive disorder were identified. A further 13 patients had transient periods of depressed mood, while the majority of patients showed no clear evidence of depression. The BDI was found to be valid in this group of patients.

Depressed mood is thought to be common after spinal cord injury (SCI), but the nature of this mood disturbance is debated. Many consider that it is only to be expected that those with SCI will be depressed, and that lowered mood is a normal response to the injury (Witthower *et al*, 1954; Stewart, 1977*a*; Bracken & Shepard, 1980). Some consider it to be inevitable (Hohmann, 1975; Stewart, 1977*b*). Studies suggesting that depressed mood is common have been largely based on anecdotal descriptions of patients, not empirical evidence. Lowered mood may be a normal or understandable response to SCI, may be part of 'normal' grief, or may be indicative of a depressive illness. Recent clinical studies have suggested that depression may be less common than previously thought (Lawson, 1978; Fullerton *et al*, 1981). Our own experience suggests a significant number of patients suffer from depressive illness following SCI, and that this can be differentiated from other forms of lowered mood (Judd *et al*, 1986). The following pilot study prospectively examined the prevalence of depressive illness in patients following acute SCI, and assessed the utility of a standard depression rating scale in their assessment.

Method

The Austin Hospital Spinal Injuries Unit admits all patients from Victoria, Tasmania, and the southern Riverina area of New South Wales who sustain a traumatic SCI. All English-speaking patients older than 18 years, who sustained a traumatic SCI, and who did not have a significant head injury or pre-existing psychiatric or organic mental disorder, were asked to participate in the study.

All patients were admitted to the Spinal Injuries Unit within 24 hours of their accident. Each patient was interviewed within two weeks of admission by the liaison psychiatrist attached to the unit. Sociodemographic information, current psychiatric symptomatology, previous psychiatric, social and medical history, and general medical status were covered using the Structured Clinical Interview for DSM-III (SCID; Spitzer & Williams, 1983). Diagnoses were made according to DSM-III criteria (American Psychiatric Association, 1980), and were categorised as predating or occurring for the first time after the injury. Patients completed the Beck Depression Inventory (BDI; Beck *et al*, 1961) and the clinician completed the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Patients were then seen weekly throughout their in-patient stay in the acute medical and rehabilitation wards of the Spinal Injuries Unit by the liaison psychiatrist or psychologist and, as a screening instrument to monitor depression, completed the BDI weekly.

The BDI consists of a list of descriptive statements addressing 21 aspects of depression. Each category contains four to five statements of increasing severity. The score for each item ranges from 0 to 3, and the total score ranges from 0 to 62. Beck (1961) has reported that a cut-off point of 14 differentiates effectively between depressives and non-depressives. Any patient who scored 14 or more was reinterviewed by the liaison psychiatrist, to confirm or refute the diagnosis of a major depressive disorder (MDD), and the HRSD was repeated.

Results

Of 102 consecutive admissions to the unit, 71 patients were assessed from time of admission, through the acute and rehabilitation phases of treatment, to discharge into the community. Patients not included in the study were those: aged less than 18 years ($n=6$), with conversion disorder ($n=4$), with severe head injury or prolonged organic brain syndrome ($n=4$), with schizophrenia ($n=3$), with early (less than one month) neurological recovery ($n=4$), with poor English ($n=1$), deceased soon after admission ($n=3$). One patient had a MDD (DSM-III) predating the injury, and sustained his injury when attempting suicide. In addition, five patients refused to participate in the study.

The 71 patients (52 men) participating in the study ranged in age from 18 to 69 (mean 31.4) years; 41 were paraplegic and 30 were quadriplegic, and all had sustained their injury as the result of trauma.

TABLE I
Distribution of BDI scores

BDI	*Paraplegic (n=41)*		*Quadriplegic (n=30)*		*Total*
	Male	*Female*	*Male*	*Female*	
Consistently <14 (not depressed)	18	7	14	5	44 (62%)
Isolated >14 (understandable dysphoria)	7	2	3	1	13 (18%)
Persistently >14 (depressive illness)	5	2	5	2	14 (20%)

Weekly evaluation throughout the acute treatment and rehabilitation phase showed three clear patterns. Forty-four patients consistently scored less than 14 on the BDI, and showed no evidence at clinical interview of depressive illness, although transient periods of dysphoric mood were noted. A second group (13 patients) had isolated scores of more than 14 on the BDI, and detailed psychiatric reassessment at this time confirmed lowered mood. Rather than being indicative of a depressive illness, their increased dysphoria appeared to be the result of social factors (e.g. separation from family) and complications of the injury (e.g. poorly controlled pain). In this group the dysphoria was transient, and resolved following psychotherapeutic intervention and correction of the identified causative factors. In a third group (14 patients) the BDI was persistently elevated (>3 weeks, BDI>14), and MDD was confirmed at reassessment (Table I).

Details regarding the patients who developed MDD are shown in Table II. The 14 patients (ten men) ranged in age from 18–51 (mean 31.6) years. Seven were paraplegic and seven were quadriplegic. One patient had a past history of MDD and two of dysthymic disorder. Vulnerability factors identified in six other patients are listed in Table II. Similar factors were observed less frequently in the other two patient groups (3 of 13 and 11 of 44 patients). Onset of depressive illness was 3–40 weeks after injury. Scores on the HRSD (17 items) at the time of diagnosis ranged from 18 to 30 (mean 24.4). All patients identified as having MDD were treated with supportive psychotherapy, and prescribed antidepressant (tetracyclic and tricyclic) medication, initiated when clinical reassessment confirmed the diagnosis of MDD, following persistently elevated BDI scores. Thirteen of the patients improved with treatment (mean BDI at discharge=8), and for eight this improvement was evident within four weeks of prescription of medication, and appeared to be directly attributable to the medication. One patient with persistent symptoms required in-patient care in the psychiatric unit. Four patients, although markedly improved with treatment, continued to experience episodic mild exacerbations of their mood disturbance. One patient refused antidepressant medication and remained significantly depressed (BDI score of 20) when discharged to out-patient follow-up.

TABLE II
Patients with major depressive disorder

Age	*Sex*	*SCI*	*Vulnerability factor*	*Diagnosis of major depressive disorder*			
				No. of weeks admission	*Ward*	*BDI score*	*HRSD score*
47	F	L1	Past history of anxiety	3	AT[1]	16	24
49	F	T4	Schizoid personality traits	4	AT	15	18
51	F	C5	Past history of MDD	4	AT	18	26
41	M	T6	None detected	5	AT	18	25
19	M	T11	None detected	6	AT	43	30
28	M	C6	Past history of dysthymic disorder	8	AR[2]	24	26
22	M	C5	Past history of polydrug abuse	10	AR	22	24
51	M	C7	None detected	10	AT	18	22
34	M	C6	Past history of dysthymic disorder	12	AR	20	24
21	M	T8	Past history of alcohol abuse	14	AT	19	24
19	M	T11	Family conflict	16	AR	33	28
24	M	L3	Wife killed in accident	22	AR	17	23
19	F	C5	None detected	24	AR	14	18
18	M	C4	None detected	40	AR	14	24

1. Acute medical treatment.
2. Active in-patient rehabilitation.

Discussion

Two main issues were examined in this study, the first concerning the prevalence of depressive illness following SCI. Methodological problems have made studies of the nature and prevalence of depression in the physically ill difficult to interpret. Particular difficulties are that heterogeneous subject populations have been studied, there has been a lack of clarity regarding the definition of cases, and an absence of assessment measures that have been standardised in medically ill patients. Available studies suggest that the prevalence of depressive illness in patients with medical illness varies from 5% to 30% (Schwab *et al*, 1967*a*,*b*; Stewart *et al*, 1965; Porter, 1970; Glass *et al*, 1978; Neilsen & Williams, 1980). Five per cent is no different from the general population, while 30% is five to six times the expected rate.

In the present prospective study of a population homogeneous with respect to physical illness, using a two-stage process for assessment of depression and DSM–III diagnostic criteria, we found that the majority of patients experienced mild and transient periods of low mood, which could be considered a 'normal' response to the losses due to SCI. Some patients experienced transient, more severe mood disturbance in the context of medical or interpersonal and social problems, but these could also be regarded as normal and understandable. A second discrete group, comprising 20% of patients, developed MDD, and were readily distinguished from those with 'normal' or 'understandable' responses. This finding is similar to that for other groups of medically ill patients, and while some studies suggest a higher prevalence of depressive disorders in SCI, it is consistent with the findings of Fullerton *et al* (1981), who found 30% of patients developed major or minor depression (according to Research Diagnostic Criteria) after injury.

Depressive disorders occurred with similar frequency in paraplegics and quadriplegics (17% v. 23%). This pattern does not fit well with the common view that as severity of injury increases, so does the risk of depression. The sex ratio for those with depressive disorders was equal to the overall ratio of male : female patients (5:2). Personality, interpersonal, and illness variables suggesting vulnerability to depression were significantly more frequently identified in those developing a depressive illness, as revealed by χ^2 analysis ($\chi^2=8.27$, $P<0.05$). The time of onset of depressive illness varied widely, perhaps suggesting the involvement of diffuse aetiological factors, including not only the injury and the individual's response to it, but also interpersonal and social consequences of the injury, as well as possible neurophysiological and neuroendocrine changes. It should be noted, however, that our study assessed patients only during the acute treatment and active rehabilitation stages. More patients may develop a depressive illness during rehabilitation into the community, consequent upon the stress of re-establishing family, social, and vocational roles.

Although all patients were treated by supportive psychotherapy, antidepressants, and the medical and rehabilitation therapies, recovery from depression appeared to be clearly related to the antidepressant medication. Seven patients developed a MDD during the acute treatment phase and of these, five showed a marked response to antidepressant treatment before transfer to the active rehabilitation phase. Seven patients developed a MDD during their rehabilitation, and improvement did not appear to be linked to particular events in their rehabilitation course. This is in contrast to the 13 patients with isolated BDI scores greater than 14, where the development and resolution of dysphoria often did appear to be related to particular medical treatment events.

The second issue examined concerned the utility of a standard depression rating scale in the assessment of patients following SCI. The BDI appeared to be a valid measure of depressive illness in this group of patients. A cut-off point of 14, as previously used by Moffic & Paykel (1975) in medical in-patients, was used in this study. We found both the degree and persistence of BDI score to be of diagnostic use. Patients consistently scoring greater than 14 were diagnosed as suffering from a MDD, while those with isolated elevated scores did not receive this diagnosis. It has previously been suggested that the heavy weighting of the BDI with items such as pessimism, sense of failure, and sense of punishment makes it particularly suitable for use in the medically ill. We found that items most likely to distinguish between depressed and non-depressed patients were sadness, somatic preoccupation, anorexia, pessimism, guilt, irritability, and suicidal ideas. Although somatic preoccupation, anorexia, and insomnia were common in both depressed and non-depressed patients, they were qualitatively different and more severe in those with a depressive illness. Certain items, for example weight loss, occurred in all SCI patients, and thus were not of discriminative value.

In conclusion, the results of this study do not substantiate earlier observations that all patients with SCI experience depression, but they do suggest that a substantial proportion of patients suffer from a depressive illness distinct from the normal response to SCI. Furthermore, we have indicated that this group can be readily identified by systematic evaluation of patients using conventional interview techniques and rating scales, and that such patients do respond to treatment with antidepressant medication. Further studies to confirm and extend these findings are indicated.

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A Rating Scale for Drug-Induced Akathisia

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A rating scale for drug-induced akathisia has been derived that incorporates diagnostic criteria for pseudoakathisia, and mild, moderate, and severe akathisia. It comprises items for rating the observable, restless movements which characterise the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. A standard examination procedure is recommended. The inter-rater reliability for the scale items (Cohen's κ) ranged from 0.738 to 0.955. Akathisia was found in eight of 42 schizophrenic in-patients, and nine had pseudoakathisia, where the typical sense of inner restlessness was not reported.

Akathisia is probably the commonest and one of the more distressing of the movement disorders associated with antipsychotic drugs (Lancet, 1986; Barnes, 1987). Following the original descriptions of drug-induced akathisia (Sigwald *et al*, 1947; Steck, 1954), there was little further work on the phenomenology of akathisia, and no consistent or clear operational definition emerged. The diagnosis of akathisia tended to rest upon systematic questioning regarding a patient's inner restlessness. However, reliance on a patient's subjective report alone does not allow for reliable diagnosis (Van Putten & Marder, 1986, 1987).

The lack of delineation of the associated motor behaviour created difficulty in separating akathisia from other movement disorders seen in drug-treated schizophrenic patients. These include Parkinsonian tremor, dystonia, tardive dyskinesia, tics, stereotypies and mannerisms. The distinction between tardive dyskinesia and akathisia is complicated by the common coexistence of the two conditions (Barnes *et al*, 1983). Descriptions of tardive dyskinesia have consistently mentioned motor restlessness, and subjective distress has been found to correlate rather better with trunk and limb movements than with orofacial movement (Rosen *et al*, 1982).

The lack of diagnostic criteria may partly account for the wide range of prevalence figures reported in the literature (Marsden *et al*, 1985): although a figure of around 20% is commonly accepted (Ayd, 1961; Braude *et al*, 1983), Freyhan (1958), for example, found a prevalence of only 12.5%, while Van Putten (1975) recorded a figure of 45%. Furthermore, in a sample of drug-free schizophrenic patients who received haloperidol (10 mg) at bedtime for seven days, Van Putten *et al* (1984) found that 75% experienced akathisia.

In addition, the absence of a precise clinical definition might be partly responsible for the failure of clinicians to recognise the condition consistently (Weiden *et al*, 1987). It may also contribute to the common misinterpretation of motor phenomena of akathisia as the signs and symptoms of psychiatric illness (Van Putten, 1975; Braude *et al*, 1983). If akathisia is misdiagnosed as an exacerbation of agitation or psychotic excitement, this error may prompt an increase in antipsychotic drug dose, which would almost certainly aggravate the problem.

Validity of the scale

The validity of the rating scale (see Appendix) derives from its basis in signs and symptoms found to be characteristic of the condition in our previous studies of both acute psychiatric admissions receiving antipsychotic medication (Braude *et al*, 1983) and schizophrenic out-patients on maintenance medication (Barnes & Braude, 1985).

Subjective item

These studies found that against the background of a relatively non-specific sense of inner restlessness or mental unease, sufferers were often particularly aware of tension and discomfort in their limbs, sometimes with paraesthesia and unpleasant pulling or drawing sensations in their legs. These complaints are akin to symptoms found in the 'restless legs', or Ekbom's, syndrome (Blom & Ekbom, 1961; Lancet, 1986).

In addition, the patients with akathisia would typically experience a desire to move, an awareness that they were unable to keep their legs still, or a compulsion to move which was often particularly referable to the legs. Many patients complained that the condition was least tolerable when they were required to stand still, for example when queueing for meals or medication on the ward, waiting at the supermarket checkout, or standing in the kitchen while cooking. These symptoms constitute the subjective diagnostic criteria for akathisia included in the item 'awareness of restlessness' of the scale.

The inner restlessness and emotional unease experienced by patients with akathisia is often distressing for patients, and may lead them to refuse further medication. The importance of akathisia as a cause of poor compliance with antipyschotic drugs has been emphasised by Van Putten (1974). The overwhelming and intense nature of the subjective experience in severe cases is illustrated by reports where akathisia has been thought to have contributed to violent, aggressive behaviour (Kekich, 1978; Kumar, 1979; Schulte, 1985) or impulsive suicidal behaviour (Shear *et al*, 1983; Schulte, 1985; Drake & Erlich, 1985; Shaw *et al*, 1986). An item for distress related to restlessness was included in the scale. Any distress associated with akathisia can usually be elicited without difficulty, and is commonly complained of spontaneously.

Objective criterion

The study by Braude *et al* (1983) and a similar investigation by Gibb & Lees (1986) also found that particular patterns of restless leg movements were observed in association with the subjective experience of akathisia. The most characteristic signs that emerged were rocking from foot to foot or walking on the spot when standing. Van Putten & Marder (1987) agree that these foot movements are easily recognisable, and are present in all patients with moderate or severe akathisia. Braude *et al* (1983) observed other patterns of restless movement in seated patients, which accompanied the typical subjective experience of akathisia. They described these as shuffling or tramping of the legs. With severe akathisia, patients appeared to be unable to stand without walking or pacing. Gibb & Lees (1986) generally confirmed these findings, and suggested further that fast walking and swinging of one leg when sitting should also be considered as part of the akathisia syndrome.

These motor phenomena were considered to be observable diagnostic criteria for akathisia, and are included in the 'objective' item of the rating scale.

Global item

The rating of 'absent' refers to the failure of the rater to elicit any subjective awareness or complaint of restlessness. However, in the absence of any report of a sense of inner restlessness or a compulsion to move, some patients may manifest obvious, complex, repetitive movements resembling those seen in akathisia (Barnes & Braude, 1985). A common feature is rocking from foot to foot while standing. These movements seem to be of a volitional rather than choreic nature, and appear to represent motor restlessness. This syndrome has been called pseudo-akathisia (Munetz & Cornes, 1982; Barnes & Braude, 1985), and its relationship with akathisia and tardive dyskinesia is a matter for speculation (Barnes & Braude, 1985; Stahl, 1985; Munetz, 1986).

The signs of motor restlessness are not invariably present in mild cases of acute akathisia (Braude *et al*, 1983). The typical subjective experience of akathisia in the absence of restless movements has been referred to as 'subjective akathisia' (Van Putten & Marder, 1986). In practice, it may be difficult to differentiate between this condition and subtle manifestations of anxiety or emotional distress unrelated to akathisia. This difficulty is acknowledged by the 'questionable' rating in the global item of the scale, and the existence of subjective akathisia is reflected in the 'mild akathisia' rating, as it does not demand the presence of the characteristic restless phenomena.

The ratings for moderate, marked, and severe akathisia reflect increasing degrees of subjective distress and the desire or compulsion to move, an increasing inability to remain sitting comfortably, and an increasing amount of time spent exhibiting restless movements, such as rocking from foot to foot when standing, and pacing up and down.

Reliability

Patients and method

Forty-two chronic in-patients, all of whom fulfilled DSM-III criteria (American Psychiatric Association, 1980) for schizophrenia, and were receiving antipsychotic medication, were each assessed by two raters during the same examination period using the rating scale (Barnes & Halstead, 1988). The age range of the sample was 32–65 (median 52) years, and 13 were women.

Examination procedure

Each patient was observed seated for at least five minutes while consent to take part in the study was obtained and the patient completed a self-rating scale for anxiety, modified from the Leeds Anxiety Scale (Snaith *et al*, 1976). The patient was then asked to stand up, and was examined for evidence of Parkinsonism using the Extrapyramidal Rating Scale (Simpson & Angus, 1970). Still standing, patients were then engaged in conversation on neutral topics for several minutes while being observed, and finally were asked specific questions about inner restlessness, and awareness of the features of akathisia. For example, inquiry was made as to whether they experienced a sense of inner restlessness, and whether restless, fidgety feelings could

TABLE I
Inter-rater reliability

Rating scale item	*Linearly weighted Cohen's* κ
Objective	0.738
Subjective	
Awareness of restlessness	0.827
Distress related to restlessness	0.901
Global clinical assessment	0.955

be localised to any part of their body. Further, they were asked if they had any awareness of difficulty sitting comfortably for long periods, an increasing restlessness and tension when required to stand still, or a compulsive desire to move.

If akathisia was present, additional information was collected regarding any diurnal variation of symptoms, and whether the patient was aware of any particular situations which seemed to provoke or exacerbate the restlessness and any associated distress.

Inter-rater reliability

The agreement between the two raters on the akathisia scale was calculated. There was high inter-rater reliability on the scores for the four items, expressed in terms of Cohen's κ (Table I).

There was complete agreement between the two raters on the presence of akathisia, that is a rating of two or more on the global clinical assessment item. There was disagreement between the raters on the scores for the severity of akathisia in only two patients. The scores differed by one in both cases.

According to the global rating, akathisia was found in eight (19%) of 42 patients. The condition was rated as being of mild or moderate severity in six patients, and marked or severe in only two. Five (12%) of the 42 patients received a rating of 'questionable' akathisia. They manifested non-specific restless movements and described a vague sense of inner tension, but these features were unconvincing for a diagnosis of akathisia.

Nine (21%) patients were rated as having pseudoakathisia. These patients exhibited akathisic movements, that is, they scored one or more on the 'objective' item, but did not apparently experience any associated inner restlessness or desire to move their legs, that is, they scored 0 on the 'subjective' item.

Discussion

In this small reliability study, the rating scale was found to be viable and practical, and a high level of inter-rater reliability was achieved. The results confirm both the relatively high prevalence of akathisia in chronic schizophrenic patients receiving maintenance antipsychotic drugs, and the existence in a proportion of such patients of pseudoakathisia, where the characteristic movements of akathisia are observed in the absence of the subjective symptoms.

It is envisaged that the rating on the global item alone should be sufficient for diagnostic purposes, and for measuring change in the overall severity of akathisia in response to treatment. Nevertheless, to rate the global item accurately the elements of the three other items need to be taken into account, and these items should be completed first.

The individual ratings on the two subjective items, 'awareness of restlessness' and 'distress related to restlessness', and the 'objective' item may be of value if an investigator wishes to detect whether the objective and subjective components of akathisia are differentially affected by particular drug treatments, or change independently over time. Also, when assessing a patient with pseudoakathisia, either over time or in the context of a treatment trial, the main measure of the condition is the rating on the 'objective' item. However, the emergence of a score for the 'awareness of restlessness' item might warrant a change in diagnosis to akathisia.

It is recommended that the scale is completed after observation of the patient in more than one setting. Preferably, the patient should be unobtrusively watched in a natural setting, for example while involved in activity on the ward, as well as during a formal interview. Experience with the assessment of patients with akathisia suggests that the situation in which the characteristic restless movements of rocking from foot to foot or treading on the spot are most likely to be observed is when the patient is standing with the rater, engaged in casual conversation on some neutral topic.

We are currently using this scale in a placebo-controlled study of β-adrenoceptor-blocking drugs in akathisia, and in a prevalence study in a population of chronic schizophrenic in-patients. The scale is also being employed in studies by other research groups in the UK and internationally. We plan to examine the reliability of the scale further in these studies, and also hope to test the validity of the scale by using an electronic movement meter to quantify the restless activity of patients, to provide an objective measure of the condition.

Appendix: Rating scale for drug-induced akathisia

Patient name:
Patient research no.:
Hospital no.:
Ward:
Rater:

Patients should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example, while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg, while sitting, *and/or* rocking from foot to foot or 'walking on the spot' when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 The patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed.

Subjective

Awareness of restlessness

0 Absence of innser restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of an intense compulsion to move most of the time *and/or* reports a strong desire to walk or pace most of the time

Distress related to restlessness

0 No distress
1 Mild
2 Moderate
3 Severe

Global clinical assessment of akathisia

0 Absent
No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 Questionable
Non-specific inner tension and fidgety movements
2 Mild akathisia
Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress
3 Moderate akathisia
Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4 Marked akathisia
Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing
5 Severe akathisia
The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

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Quality of Parenting in Alcoholics and Narcotic Addicts

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Alcoholics and heroin addicts were compared with a normal control group to determine whether there were differences in quality of parenting during childhood, assessed using the Parental Bonding Instrument. Maternal and paternal overprotection were reported more commonly by narcotic addicts. Maternal overprotection alone was implicated in alcoholics. Narcotic addicts seem to have more disturbed parenting than alcoholics, especially paternal parenting.

While the social aetiology of both alcohol dependence and heroin addiction is far from clear, there is evidence that both childhood and contemporary environmental factors may be involved in both conditions. The impact of early family environment has however been poorly delineated. For narcotic addicts, 'broken homes' (parental separation or divorce) are reported as an aetiological factor (Stimson, 1973), and 'disruptive events' in childhood, such as family violence, hospitalisation, and other separations, are also common (Rousaville *et al*, 1982). In one review of the literature on parenting patterns of narcotic addicts, mothers are described as "indulgent and over-protective", and fathers as "weak and ineffectual" (Ben-Yehuda & Schindell, 1981). In the case of alcoholics, early research also drew attention to their unstable family environments (McCord & McCord, 1960; Robins, 1966). A recent prospective study found that low warmth and poor cohesion in the family predicted alcoholism in blue-collar workers but not in college graduates (Vaillant, 1980).

The relation of specific parenting qualities to alcoholism and narcotic addiction has not been assessed in any reliable, structured manner, but the development of reliable and valid instruments assessing family characteristics has made such research now possible. The Parental Bonding Instrument (PBI), developed by Parker *et al* (1978) to measure parenting qualities, yields two broad dimensions, 'care' and 'protection', for both mothers and fathers. The construct of 'care' involves, at one extreme, affection, warmth and empathy, and at the other, coldness, indifference, and rejection. The construct of 'protection' involves parental control, overprotection, intrusion, and infantilisation at one extreme, and promotion of independence and autonomy at the other.

The present study uses the PBI to assess the quality of parenting reported by narcotic addicts and alcoholics, compared with normal controls. It was hypothesised that both drug-dependent groups would have a similar profile of parenting experiences to neurotic depressives (i.e. less care and greater protection, as reported by Parker (1983)). This prediction was made firstly from evidence of an association between depressive disorders and both alcoholism (Behar & Winokur, 1984) and narcotic dependence (Khantzian & Teece, 1985), and secondly from previous reports, discussed above, that disturbances in parenting in childhood are common in narcotic addicts and alcoholics.

Method

Subjects

Patients

All 110 patients referred for admission and detoxification to a Sydney drug detoxification clinic were eligibile for inclusion in the study. This clinic is a 40-bed hospital offering a medicated withdrawal regime and a short-term rehabilitation programme for both alcoholics and narcotic addicts. Subjects were included if they fulfilled DSM–III criteria (American Psychiatric Association, 1980) for either alcohol dependence or heroin dependence. Subjects were excluded if they were found to have marked memory impairment on the Mini Mental State Examination at the time of the study (Folstein *et al*, 1975), or if they had coexisting psychoses or severe depressive illness such as endogenous depression (the hospital does not accept such patients for admission).

Controls

Patients and accompanying relatives attending three Sydney general practitioners were approached and asked to complete the same questionnaires as the patient groups. In addition, this population was also screened for alcohol problems using a brief screening questionnaire; this instrument is reliable and valid (Tomson, 1985), two positive responses indicating alcohol dependence. Such patients were excluded from the study. This gave 127 controls.

We chose a single control group rather than two separate groups, one for each drug-dependent group. We believe any effect of age and sex differences in the three groups can be accounted for in the multivariate analysis.

Procedure

The following data were obtained for the patient group:

(a) personal history of drug use and prior psychiatric and medical history
(b) a Mini Mental State Examination (Folstein *et al*, 1975)
(c) sociodemographic data, including age, sex, marital status (married/common-law relationship, single, separated/divorced/widowed), country of birth (Australian, foreign born), and usual occupation (i.e. that held before significant drug problems), with occupational status categorised as professional/managerial, white collar, manual, unemployed/pensioner, or domestic duties
(d) family history of alcohol and other drug abuse
(e) the Zung Depression Inventory (Zung, 1965)
(f) the Parental Bonding Instrument (PBI) (Parker, 1983), a self-report measure that scores similarly in depressed subjects when they are both depressed and in remission; thus depressed mood *per se* does not appear to influence the subject's responses on this instrument.

Data analysis

In comparing the distribution of potential confounding variables across study groups and PBI categories, Pearson χ^2 tests (Connover, 1980) were used for discrete factors, while Kruskal-Wallis (KW) tests (Connover, 1980) were used for continuous variables. For the purpose of analysis, PBI subscales have been categorised into 'good' and 'poor'. A high score is 'good' for the care subscales, but 'poor' for the protection subscales. A high score was defined as any score above the mean of that subscale for control subjects. The cut-offs used were: 25 (maternal care), 15 (maternal protection), 22 (paternal care), and 15 (paternal protection). Since the outcomes are dichotomous, binomial methods are appropriate. Hence the relationship between study groups and PBI categories was conducted by unconditional logistic regression (Breslow *et al*, 1983). This approach allows for covariance analysis in which potentially confounding variables are controlled for.

Analyses were performed on BMDP (Dixon *et al*, 1985) and GLIM (Baker & Nelder, 1978). Two-tailed hypotheses have been used throughout.

Results

The sample

The response rate in all groups was at least 90%. The final sample comprised 70 (40 men, 30 women) narcotic addicts, 40 (31 men, 9 women) alcoholics and 127 (34 men, 93 women) healthy control subjects.

Narcotic addicts

All addicts were either daily or two-daily intravenous users. The majority used 0.5–1 g heroin each day. The period of continuous use ranged from six months to ten years, and for the vast majority was greater than 12 months. All had used other illicit drugs, and the majority had a history of multiple drug abuse preceding their heroin dependence. Most had been involved in illegal activities such as theft or prostitution. Reasons for seeking admission were pressures due to increasing tolerance to heroin, and family, financial or work pressures.

Alcoholics

Most alcoholics were daily abusers, although some described binge drinking. Ninety per cent had a diagnosis of primary alcohol dependence, and 10% gave a history suggestive of alcoholism secondary to other major psychiatric illness, including depression, agoraphobia, anxiety disorders, and schizophrenia, although at the time of admission they did not have significant affective disorder or recognisable psychosis. The Mini Mental State score on admission averaged 28 out of 30, but subsequently returned to within the normal range in all but three subjects, who showed mild to moderate impairment on further psychometric testing. Subjects included men and women who were socially adjusted (e.g. still working) as well as 'skid-row' alcoholics.

Group differences on demographic variables

The three groups were compared on demographic variables, not because of any intrinsic interest in the detail of these relationships, but simply because they might confound the relation between parenting and drug dependence; they are in a sense 'screening' analyses only.

Significantly more of the addicts and alcoholics were male than were controls ($\chi^2=16.5$, $P<0.001$; $\chi^2=30.8$, $P<0.0001$ respectively). Although a greater proportion of the alcoholics were male than were addicts, this difference just failed to reach significance ($\chi^2=3.7$, $P<0.06$).

The mean (s.d.) ages of the controls, addicts and alcoholics were 30.4 (9.2), 25.8 (5.6) and 37.9 (10.6) years respectively. There was evidence of statistically significant variation in the ages of the three groups (KW = 43.02, $P<0.001$). Controls were significantly older than addicts (KW = 13.26, $P=0.0001$) but younger than alcoholics (KW = 19.76, $P<0.0001$). Alcoholics were significantly older than addicts (KW = 38.74, $P<0.0001$).

The three groups were significantly different in their distribution by marital status (Table I).

Table II shows the distributions of the three groups by occupational status; addicts differed significantly from the other two groups. Controls generally seemed of higher occupational status than either addicts or alcoholics when one considers that over a third of controls were not employed. Alcoholics were comparable with addicts in terms of occupational status.

There were no significant differences in the controls, addicts or alcoholics in terms of proportion of Australian to foreign born, with 81%, 74% and 75% respectively being born in Australia.

TABLE I
Distribution of groups by marital status

	Controls (%) (n = 127)	*Addicts (%) (n = 70)*	*Alcoholics (%) (n = 40)*
Single	26	67	35
Married/ common-law relationships	58	23	25
Separated/ divorced	16	10	40

Addicts v. controls $\chi^2 = 32.0$, $P<0.0001$.
Alcoholics v. controls $\chi^2 = 15.7$, $P<0.001$.
Addicts v. alcoholics $\chi^2 = 14.9$, $P<0.001$.

TABLE II
Distribution of groups by 'usual' occupational status

	Controls (%) (n = 127)	*Addicts (%) (n = 70)*	*Alcoholics (%) (n = 40)*
Professional/ managerial	13	9	18
White collar	31	21	20
Manual	17	66	56
Unemployed/ pension	2	3	3
Domestic duties	37	2	3

Addicts v. controls $\chi^2 = 53.4$, $P<0.0001$.
Alcoholics v. controls $\chi^2 = 2.1$, $P>0.05$.
Addicts v. alcoholics $\chi^2 = 30.2$, $P<0.0001$.

The relation of demographic variables, PBI and depression scores

Parental Bonding Instrument

Sex, marital status, occupational status and country of birth were not significantly related to PBI subscale scores (maternal care, maternal protection, paternal care or paternal protection) when assessed by χ^2 analyses. Age was significantly associated with maternal care (KW = 5.76, $P = 0.02$) and maternal protection (KW = 6.97, $P = 0.008$).

Zung Depression Scale

Men had higher depression scores (mean 50.4, s.d. 8.4) than women (mean 47.6, s.d. 7.6) (KW = 5.86, $P = 0.02$). This finding is probably attributable to the greater proportion of males in the patient groups, the latter having generally higher levels of depression than healthy controls. There was no significant association between depression and country of birth, or age. There was a significant relationship between depression and marital status (KW = 22.52, $P = 0.0004$), mean (s.d.) Zung scores being for single subjects 50.1 (7.4), for married/common-law relationships 46.8 (8.2), and for those separated/married/divorced 49.2 (9.3). There was also a significant difference in depression according to occupational status (KW = 12.5, $P = 0.006$); mean scores in the groups from higher to lower status respectively were 47.5, 46.9, 51.8, 49.2, and 46.1. Comparison of depression scores between normal and abnormal categories of the care and protection scores indicated that depression scores were related significantly to both maternal protection (KW = 5.71, $P = 0.02$) and paternal protection (KW = 7.42, $P = 0.006$), but not to maternal care (KW = 1.28, $P = 0.3$) or paternal care (KW = 1.93, $P = 0.2$).

Group differences in depression

Mean (s.d.) depression scores in addicts, alcoholics and controls were 54.3 (8.0), 51.9 (8.2) and 44.3 (5.5) respectively; there was a statistically significant variation in depression scores in these three groups (KW = 72.54, $P<0.0001$). Scores were not significantly different in addicts and alcoholics (KW = 2.63, $P = 0.1$), but both alcoholics (KW = 25.9, $P<0.0001$) and addicts (KW = 63.81, $P<0.0001$) were significantly more depressed than controls. This can be attributed to their drug abuse, and is not due to any confounding by sex since, contrary to most data (see Bebbington, 1978), our findings showed men to be more depressed than women; we believe this is because our drug abusers were more often men.

Group differences in PBI scores

A significantly greater proportion of narcotic addicts had high (above the mean for controls) maternal and paternal protection scores than controls, but these two groups were not significantly different on either care variable. A significantly greater proportion of alcoholics had high maternal protection scores than controls, but there were no significant differences on the other PBI indices. The proportions of alcoholics and narcotic addicts with high scores did not differ significantly on any of the four indices (Table III).

With the exception of age (which was associated with both group status and some PBI indices) we believe the above findings are not confounded by demographic variables. There are, however, other variables which might have influenced the relation of PBI scores to alcoholism or addiction by virtue of being associated with both. The first of these is a family history of alcoholism, which was more common in alcoholics (62%) ($\chi^2 = 12.1$, $P<0.001$) and addicts (41%) than controls (29%), although the latter difference was not statistically significant. Family history of alcoholism was also significantly associated with lower paternal care scores ($\chi^2 = 5.07$, $P = 0.02$), although not with other PBI indices. Those with a family history of alcohol abuse also had lower maternal care scores and higher protection scores, but these differences failed to reach statistical significance. In contrast, a family history of other drug abuse did not significantly differentiate either alcoholics or addicts from controls; neither was it associated with PBI subscale scores.

Thus it is possible, although unlikely, that the associations between the PBI indices and both alcoholism and addiction

TABLE III
Group differences in parental bonding scores

PBI scale	*Alcoholics (n = 37)* n	*(%)*	*Controls (n = 127)* n	*(%)*	*Addicts (n = 70)* n	*(%)*	χ^2	P
Maternal care	17	(45.9)	73	(57.5)	35	(50.0)	2.00	0.4
Maternal protection	13	(35.1)	74	(58.3)	30	(42.9)	8.17	0.02
Paternal care	16	(43.2)	62	(51.7)	25	(37.9)	3.41	0.2
Paternal protection	19	(51.4)	66	(55.0)	26	(39.4)	4.19	0.1

Cell entries are numbers of subjects (with percentages of the group total in parentheses) in the 'good' category (high for care and low for protection).
The χ^2 test and associated P value test the null hypothesis of equality of distribution of subjects in high and low categories between the three groups of subjects.

TABLE IV
Multivariate analyses

Confounder	*Maternal care*	*Maternal protection*	*Paternal care*	*Paternal protection*
(a) Narcotic addicts v. controls				
None	1.2	4.31	3.28	4.17
	(0.3)	(0.04)	(0.07)	(0.04)
Age	2.71	5.81	3.86	5.21
	(0.1)	(0.02)	(0.049)	(0.02)
Zung score	0.06	0.61	0.59	0.43
	(0.8)	(0.4)	(0.4)	(0.5)
Family	1.18	4.40	2.81	4.14
alcohol	(0.3)	(0.04)	(0.09)	(0.04)
All	0.62	1.20	0.79	0.80
	(0.4)	(0.3)	(0.4)	(0.4)
(b) Alcoholics v. controls				
None	2.74	8.20	0.96	0.24
	(0.1)	(0.004)	(0.4)	(0.6)
Age	0.93	5.57	0.57	<0.01
	(0.3)	(0.02)	(0.5)	(1.0)
Zung	1.46	4.13	0.50	0.24
	(0.2)	(0.04)	(0.5)	(0.6)
Family	2.37	6.83	0.06	0.98
alcohol	(0.1)	(0.009)	(0.8)	(0.8)
All	0.25	2.12	<0.01	0.98
	(0.6)	(0.1)	(1.0)	(0.3)

Note that cell entries are likelihood ratio statistics, with one degree of freedom and P values in parentheses.

are spurious, and simply reflect two other relationships, being on the one hand the genetic predisposition to alcohol and drug abuse (in those subjects with a family history of alcoholism), and on the other that parental alcohol abuse alone affects parenting. Under these circumstances it is conceivable, but improbable, that there is no direct relationship between parenting and drug abuse.

The second potentially 'confounding' variable is depression, being significantly related to some PBI subscale scores and more frequent in alcoholics and addicts than in controls. However, clearly, if depression were the result of drug dependence (as we believe), it should not be controlled as a confounding variable.

Multivariate analyses were thus performed to assess the proportions of subjects in the various PBI groups, taking into account the above-mentioned potentially 'confounding' variables of age, depression, and family history of alcoholism, the latter two being included more for reasons of absolute methodological rigour than for substantial practical reasons, as we have discussed. Thus if significant differences were 'masked' in the univariate analyses, this would be revealed in the multivariate analyses.

Multivariate analyses

In these analyses, the univariate results, which performed the same function, are modified by controlling for the three potentially confounding variables which were discussed previously.

Narcotic addicts versus controls

There was substantial evidence that narcotic addicts differed from control subjects in terms of distribution between protection categories, both maternal and paternal (Table IVa). Only after controlling for depression (Zung score) did the difference cease to reach statistical significance. On the other hand, Table IVa confirms the univariate funding that there was little evidence of a difference in care category distribution between these two groups. Adjusting the difference in paternal care for age shows marginal significance, although given the number of tests conducted, this result should not be given too much emphasis.

Alcoholics versus controls

The primary difference between alcoholics and controls also appears to lie in the protection category, although in this case only maternal protection (Table IVb). However, none of the potential confounding variables considered accounts for the difference in alcoholic and control categorisation until all three are controlled for simultaneously. Table IVb confirms the univariate finding that there is little evidence of differences in care category distribution between alcoholics and controls, both maternal and paternal.

Discussion

A major problem, highlighted by Vaillant (1983), in researching the family environment of alcoholics is that the genetic effect of having an alcoholic parent is not usually accounted for. Our findings support Vaillant's caution, since parental care in alcoholics was significantly related to a family history of alcoholism. Thus in evaluating the relationship between parenting and both alcoholism and narcotic addiction, the effects of family history of alcoholism were taken into account. This we believe is a conservative approach methodologically, since at least some of the influence of family history of alcohol on parenting is likely to be the result of environmental factors, in addition to any genetic effect as argued by Vaillant. Thus any positive associations between parenting and alcoholism or narcotic addiction found in this study after controlling for a family history of alcoholism can be expected to be very robust reflections of any environmental effect.

Similarly, we find depression is associated with both indices of poor parenting and with alcoholism and narcotic abuse. This three-way association may be explained in a number of ways. The first is that poor parenting independently contributes to both depression and drug dependence (and clearly the latter two variables are inter-related). The second is that poor parenting contributes to depression, which in turn predisposes to drug dependence (i.e. depression is a mediating variable). Thirdly, it is possible that poor parenting is related to drug abuse, of which depression is a consequence. Finally, there may be some combination of the above.

In the first two instances there is some indication for controlling for the effects of depression, since we are most interested in whether parenting affects drug dependence *per se* (there is already good evidence to suggest it does affect depression - see Parker (1983). In the third instance there would be no indication for controlling for depression; indeed to do so would likely lead to some suppression of the relation between parenting and drug dependence. Our own data indicate that the third possibility does at least exist, and may be the most likely explanation, since more than 90% of the sample were diagnosed clinically as having depression secondary to their drug abuse. Because we cannot entirely exclude that the first two possibilities may also operate, we control for depression but we believe to do so is unnecessarily conservative statistically. The danger with this approach is that we lose useful information.

Parenting and narcotic addiction

Univariate analyses indicated significant differences between narcotic addicts and healthy controls on selected PBI variables, the former demonstrating higher maternal and paternal protection scores. When the independent effects of either age or a family history of alcoholism were taken into account, the association between maternal and paternal protection scores and narcotic addiction remains significant. When the effects of depression are taken into account, the relationship between protection scores and addiction is no longer significant. These findings suggest that maternal and paternal overprotection, independent of other variables (apart from depression), are related to narcotic addiction.

These findings are consistent with the 'overprotection hypothesis' for the aetiology of narcotic addiction (Blechman, 1982). It is possible that overprotective maternal and paternal parenting encourages dependency in the child; dependent personalities may in turn be more prone to narcotic dependence. The findings seem less supportive of a hypothesis suggesting mediation through antisocial behaviours as we might have expected low care scores, and this was not observed.

Parenting and alcoholism

In univariate analyses the only significant difference between alcoholics and controls concerned maternal overprotection. This relationship remained significant even when age, family history of alcoholism, and depression were separately controlled. Thus maternal overprotection seems to have a role in the development of alcoholism. The possibility is that overprotection may contribute to dependent traits and subsequent alcohol abuse.

Summary

It would appear that maternal overprotection has an effect on both narcotic addiction and alcoholism; in the latter instance the relationship seems more substantial, being significant even when depression is accounted for. Paternal overprotection has the same bearing on narcotic addiction, but not apparently on alcoholism. The findings seem to support the overprotection hypothesis in drug dependence.

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Anorexia Nervosa in Hong Kong

Why not More in Chinese?

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Anorexia nervosa is a geographically distinct psychiatric disorder; it is rapidly increasing in incidence in Western countries, while being virtually unreported in China, or in the Chinese community of Hong Kong. This is surprising when the Chinese preoccupation with food and their reported readiness to somatise dysphoria are considered. Three Chinese anorectics born and living in Hong Kong and exhibiting mostly typical clinical features are reported. The rarity of the disorder in the East could be related to protective biological and socio-cultural factors specific to the Chinese, and while it may become more common, anorexia nervosa is unlikely to reach Western proportions.

Anorexia nervosa is peculiar in terms of a number of epidemiological characteristics: its distribution is predominantly among young, female subjects with a middle-class background in Western societies. While these characteristics are slowly changing (Garfinkel & Garner, 1982; Pope *et al*, 1987), the distinct geographical distribution of this disorder remains puzzling. It is reported to be common in the West, probably less frequent in Russia and Eastern European countries, uncommon in Latin American countries, and virtually unknown in China (Powers & Fernandez, 1984). There is not a single paper about anorexia nervosa in the two major psychiatric journals officially published in China, apart from a case report on psychogenic vomiting in a ten-year-old girl, who was diagnosed with 'child anorexia nerversa' (Zheng, 1982). Anorexia nervosa is rare in Malaysia (Buhrich, 1981), but appears to be increasing in Japan (Suematsu *et al*, 1985). Cultural factors have been shown to be related to a higher incidence of the disorder (Pumariega, 1986).

Reports have recently been published of anorexia nervosa arising in unusual circumstances but with largely typical clinical features. Excluding male (Margo, 1987) and prepubertal (Jacobs & Issacs, 1986) anorectics, these are mostly about black subjects or patients of West Indian origin (Thomas & Szmukler, 1985), but anorexia nervosa has also been reported in the blind (Yager *et al*, 1986), Klinefelter's syndrome (Hindler & Norris, 1986), and Turner's syndrome (Larocca, 1985). Most of these subjects were born and lived in Western countries or had been under direct Western influence (e.g. the black girl in Zimbabwe reported by Buchan & Gregory (1984) received higher education in Britain), and do not allow the disorder to be examined in a culturally different milieu, where distinct attitudes to food and body weight occur.

To our knowledge, there are no specific reports of anorexia nervosa in Chinese subjects born and living in a Chinese community. Hong Kong has a population of 5.5 million, of whom 98% are Chinese. While retaining many traditional values, it is much more modern and urbanised than China. Anorexia nervosa is encountered only very rarely. Less than ten cases were treated in the past five years in the psychiatric unit of our general hospital serving a current population of 500 000, while the unpublished Shatin Psychiatric Epidemiological Survey (conducted in 1984–86 by the Psychiatric Epidemiology Unit of the Department of Psychiatry, Chinese University of Hong Kong), using the Diagnostic Interview Schedule (DIS), revealed only one possible case (she had a concomitant diagnosis of major depression which could have been the primary disorder) out of a community sample population of 7229 subjects (3786 female, 3443 male) in the age range 18–64. We report three Chinese anorectics born and living in Hong Kong, and explore the biological and socio-cultural factors that might be related to the rarity of the disorder.

Case histories

Case 1

Miss C, aged 16, height 160 cm (5 ft 3.5 in), ideal body weight (for Chinese) 47.5 kg, was a single form-5 student referred by a private gynaecologist for severe weight loss of 40%, from 47 kg to 28.5 kg over the past year. According to her parents, Miss C had always been fussy about food. In the past year she had obvious preference for vegetables, and shunned meat and fatty food. She would use tissue paper to wipe away the film of oil attached to food, and enjoyed using a diversity of seasoning for the dwindling amount of food she took. Later she avoided having meals with her parents (unusual for Chinese families) or attending social occasions, especially those associated with eating. She also developed amenorrhoea, constipation, cold intolerance, and a recurring bilateral ankle oedema. At this point she was reluctantly taken to see a general practitioner, but was only given some vitamins.

Miss C had become very socially withdrawn, and school was her sole reason for going out, although she continued to do 20 minutes of daily exercise. She became more irritable, and despite her apparent industry, her school performance deteriorated. When the certificate examination was finally over, she weighed only 28.5 kg. There was no history of binge-eating, vomiting, or purgative abuse. A mild fear of fatness and desire to be thin were initially present, but were not later apparent to her parents. She had good past health, no history of obesity, and normal menses since the age of 13. With a quiet, introverted premorbid personality, she was deficient in social skills, sexually inexperienced, and unanimously described to be a 'good girl'. She was watched carefully by her mother, who would even escort her to and from the school, which was only one street away from home.

Her father was a 54-year-old factory owner, always busy with work, and her mother a 50-year-old housewife, with few interests other than domestic chores and her children. They described their relationship as "all right", but they had "nothing to talk about". Open conflicts were usually avoided. Miss C was the youngest of a bright sibship of four. The two elder brothers were both pursuing higher degrees in England. The sister was a plump, short girl who was academically superior, and who had left Hong Kong one year previously (just before the onset of weight loss of Miss C) to study law in England. The parents admitted to being very protective towards their children "for their own good", and had been quite upset by their departures. They turned down the wish of Miss C to study abroad because she was "too young and should wait until her siblings returned".

Physical examination showed a very cachexic girl, with dry, cold skin, and yellowish extremities. Lanugo was marked, and pubic hair was present. Blood pressure was 90/60 mmHg, and the pulse regular at 60 beats per min. Other systems were normal. Mental examination showed an alert and calm girl, who admitted to her thinness, but assumed a rather indifferent attitude to her weight loss. On more personal issues, she left her parents to do the answering for her. She denied any weight phobia or binge eating. With noticeable reluctance she suggested a target weight of 46 kg. Like her parents, she blamed the whole problem on "epigastric fullness" and examination pressures. Depressive or psychotic features were not found, and her drawings showed no overestimation of body width. Routine blood investigations were normal. The fasting levels of glucose, free T3, oestradiol, testosterone, luteinising hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH) were below normal. On TRH and LHRH stimulation tests, the low levels of sex hormones and gonadotrophins (hence the amenorrhoea) were shown to be hypothalamic in origin.

Miss C was treated with a combination of behavioural, individual, and family therapy on both an in-patient (14 weeks) and later an out-patient basis. In the ward she secretly disposed of unwanted food, and manifested resistance with sulkiness, complaints about food and noise, and attempts to divide nurses and the doctor over minor issues. Vomiting or diarrhoea was not noted. Family therapy was similarly met with resistance and denial. A visit from the patient's sister was a slight turning point, when the defences of the family loosened somewhat. Over 18 months, the family had become more spontaneous and communicative, and Miss C made a steady weight gain to 47 kg, and was performing well at school. Menstruation had not yet returned.

Case 2

Miss T, aged 23, height 155 cm (5 ft 1 in), ideal body weight 46.5 kg, was a single salesgirl who was referred from the surgical ward for unexplained weight loss of 10 kg over the past two years. She was the youngest of four children born in a working-class family in which the father was a mildly obese shopkeeper and her mother a housewife who enjoyed cooking. Family relationships were satisfactory. Miss T had an easy-going, sociable, and at times impulsive personality. She finished secondary school with fair results and later started her work as a salesgirl. Her dieting started two years previously (body weight 50 kg), when she felt distressed about looking at her "overweight look" in a photograph. Against the advice of family members, she was able to reduce her food intake significantly, to one meal per day of vegetables, fish, and soup only. Together with regular exercise, she reached 43 kg at the end of one year. Two months later, she started binging, during which she would eat very large amounts of biscuits and chocolate. This was followed by almost complete restriction of food in the next two days, but not by vomiting or diarrhoea. At about the same time, she developed right abdominal pain, which usually occurred during a meal, so that she frequently needed to stop eating and to rest in bed. Six months previously she had sought help from the surgical team, where a number of differential diagnoses (e.g. occult malignancy of the gut, mesenteric vasculitis, irritable bowel syndrome, and tuberculous gut) and extensive investigations were made. She also became amenorrhoeic, but otherwise had good past health.

Examination revealed a very thin (35 kg) but alert and cheerful young lady, who admitted to her thinness, but appeared unconcerned about her weight loss of more than 30%. She showed no depressive or psychotic features. She had mild lanugo and normal pubic hair. Rapport was readily established, and she agreed to a target weight of 45 kg, although she seemed more inclined to believe that she really had an abdominal problem. Routine and other investigations were normal. Decreased levels of oestradiol, LH, and FSH were shown on TRH and LHRH stimulation tests to be hypothalamic in origin.

Miss T was treated with individual and family therapy, but no significant psychopathology was revealed. Her profile on the Minnesota Multidimensional Personality Inventory was normal. Apart from the pain in her right iliac fossa, she was very co-operative with treatment, and made steady weight gain to 47.8 kg on discharge. Body weight, menstruation, and psychosocial functioning remained satisfactory at 18-month follow-up.

Case 3

Miss C, aged 31, height 158 cm (5 ft 3 in), ideal body weight 50.1 kg, was a single salesgirl, referred from a medical unit for progressive weight loss over the past four years. She was the youngest of five children (two male babies died soon after birth) in a working-class family in which the father had always been a distant figure, who dominated his compliant and traditional wife. He had been disappointed at the patient's inability to finish her secondary education and her meagre income as a salesgirl. The patient developed an introverted, obedient personality, and kept feelings to herself. Her eldest sister was a solitary 40-year-old single lady who "does not believe marriage works", while her elder brother had emigrated to England with his family five years previously. The patient had been left to live with her elderly parents for the past several years. There was no family history of mental illness or weight disorder. She had had a normal puberty.

Four years previously she was suddenly deserted by her boyfriend, who left for England. She then started to complain of abdominal discomfort, reduced her food intake, avoided meat and oily food, and became amenorrhoeic, socially withdrawn, and unemployed. There was no insomnia, diurnal mood variation, or suicidal thought. Despite her seeing various doctors, and despite advice from relatives, her weight continued to decrease, from 51 kg to 21.8 kg (57% loss) on presentation. There was no history of binge eating, vomiting or diarrhoea. Examination showed an extremely cachexic but alert woman, who admitted to her thinness, but expressed little concern for her weight loss. She claimed a complete lack of hunger, and blamed the weight loss on an unidentified abdominal problem. She became sulky when confronted with the repeatedly negative investigations. Her mood was low and she became transiently tearful when her four years of self-induced starvation were acknowledged. She had dry skin and bradycardia (60/min) but no other abnormal signs. Extensive investigations were normal and the endocrine disturbance was shown to be hypothalamic in origin.

In the ward she made various excuses for refusing hospital food, but secretly ate small amounts of her choice foods. She did not co-operate with nursing staff over a behavioural programme, and declined medications or intravenous fluids. In individual psychotherapy, she remained sulky, defensive, and insistent that weight gain was not going to help her "hopeless" condition. Over six months she gained only 3 kg and remained resistant to treatment, which is still in progress.

Discussion

These three cases illustrate a significant part of the spectrum of features of anorexia nervosa as described in the West. Case 1 was the classic restricting anorectic recovering with a good short-term prognosis, case 2 a bulimic anorectic with no significant psychopathology, and case 3 a 'tardive anorectic' with a poor prognosis.

Case 1 would satisfy the DSM-III-R criteria (American Psychiatric Association, 1987), with weight loss (40% below ideal weight), refusal to maintain standard body weight, and amenorrhoea. Fear of obesity was mild, and a distorted body image was not apparent. The Chinese translation for anorexia nervosa is "disease of being fed up with eating", and is a misnomer, like its English counterpart, as shown by this girl, who had a great deal of interest in food and eating, but who took very little for fear of a normal body weight, an irony that had been described by Crisp (1980). The number of aetiological factors in case 1 is impressive, and they have been well described in the Western literature (Garfinkel & Garner, 1982; Hsu, 1983). Thus, her immature, dependent personality, fastidiousness about food, middle-class overprotective parents who had a poor relationship, her youngest position in a bright competitive sibship, and major changes in the family (as the other three sibs all "fled" to England) led to a vulnerability to the disorder, at the critical time of adolescent demands, mounting school pressures, and loss of her beloved sister. In her striving for self-esteem and control, the disorder might be regarded as symbolically providing the subject with an identity, whereby the demands of adolescence were avoided by regression (Crisp, 1980). Alternatively, from a family system point of view (Minuchin *et al*, 1978), she gained power in controlling as well as maintaining the insecure parental relationship. Lacking affection from her husband, the mother was given a good reason to keep herself busy by colluding with the patient. In treatment, the patient went through a typical period required for weight gain (Crisp, 1980), the usual power struggle with ward nurses, and exhibited behaviour indicative of denial of weight phobia. She achieved a satisfactory outcome in terms of body weight, school performance and, to a lesser extent, social adjustment. The long-term prognosis is uncertain, as immediate treatment results are almost always satisfactory (Hsu, 1980).

Case 2 also satisfied the DSM-III-R criteria, with weight loss 25% below ideal weight. A moderate fear of obesity was present, but body image distortion was not obvious. In contrast to case 1, this case illustrates that anorexia nervosa in a low-risk community is not necessarily associated with other psychopathology. Mild or 'forme fruste' anorexia nervosa with no overt psychopathology has been reported to be triggered by an apparently innocuous event or comment (Garner & Garfinkel, 1980). With a fairly normal family background and no school or job pressures, the anorectic process in this patient appeared to be initiated by a simple fear of obesity and social undesirability in the easy-going personality of a woman who had had an uneventful adolescence. A degree of impulsivity and her interest in food would explain her bulimic episodes, which were followed by periods of fasting, but not vomiting, guilt, or depression. Apart from the vague abdominal pain, which could be interpreted as non-verbal resistance, she remained pleasant and co-operated with treatment.

Case 3 also satisfied the DSM-III-R criteria, with weight loss 56% below ideal weight. However, the patient did not clearly show an "intense fear of becoming fat" or "distorted body image". Aetiological factors include her growing up in a family where warmth and concern had been grossly lacking, her introverted passive personality, the departure of her brother, and the loss of her boyfriend. Her late onset, realisation of her emaciation and abnormal eating (which was not primarily aimed at the pursuit of thinness), and the associated depressive features would make her a 'secondary anorectic', whose rigid maintenance of a low body weight represents a 'pseudosolution', which gave her a false sense of identity and self-control; her displayed defiance was a defence against powerlessness and ineffectiveness (Bruch, 1982). She had a number of poor prognostic factors, including late onset, chronicity, low social class, rigid father, poor parental relationship, pervasive despair, and gross lack of motivation for treatment (Crisp, 1980).

Disturbance of body image has been noted to be a nebulous entity that may be undetectable or absent in anorectic patients (Fichter *et al*, 1986), and there have been suggestions for it to be deleted from DSM-III (Hsu, 1982). Its inconspicuousness in our patients is culturally understandable, when the rarity of obesity among Chinese girls is considered. Sensitivity to local behavioural norms and caution should be exercised in the cross-cultural application of operational diagnostic criteria (American Psychiatric Association, 1987), which may be ethnocentric to varying degrees (Ritenbaugh, 1982).

Our patients have in common their interest in food and eating, relative denial of weight phobia (partly betrayed by their behaviour), and the use of the complaint of abdominal discomfort as a reason for reduced food intake. This latter feature is understandable in the context of the reported tendency of the Chinese to somatise (Kleinman, 1977; 1980). Thus anorexia nervosa, with mostly typical clinical features and a variable loading of vulnerability factors, can occur in Hong Kong as in the West, but the question remains as to why it is still so rare. Anorexia nervosa is now usually conceptualised on a stress diathesis model of multidimensional aetiology (Piazza *et al*, 1980; Lucas, 1981; Garfinkel & Garner, 1982), which is applicable to our three patients. In the case of Blacks, Buchan & Gregory (1984) felt that psychosocial rather than biological differences accounted for the rarity of the disorder, Pumariega *et al* (1984) attributed it to "unclear fundamental differences", and Holden & Robinson (1988) felt it "has not been fully explained".

Hong Kong does not seem entirely immune from the usual list of predisposing factors for anorexia nervosa (see Garfinkel & Garner, 1982). It has in recent years undergone a great amount of modernisation and urbanisation, associated with adaptation to Western values and lifestyles. These changes could lead to increased stress reactions and psychosomatic disorders (Rin *et al*, 1966). "Performance expectations" is another factor cited (Garfinkel & Garner, 1982). The extremely competitive educational system, coupled with the high value that Chinese parents place on educational achievement (Sollenberger, 1968), was believed to result in greater anxiety among secondary school students in Hong Kong than in the United States (Cheung & Lee, 1984), and in more psychosomatic disorders (Law, 1978, 1979). The Chinese are also preoccupied with food. Offering 'good food' is a very common means of showing affection within as well as outside the family. Food is classified in a spectrum of cold (*yin*) and hot (*yang*) types, which must be balanced for good health (Koo, 1984). All these factors, together with the readiness of Chinese to somatise dysphoria (Kleinman, 1977, 1980), should have made anorexia nervosa a convenient symptom of choice for Chinese adolescents. Even when the possibility of under-recognition, especially of the less full-blown "partial syndromes" (Szmukler, 1985), is taken into account, the rarity of anorexia nervosa in Hong Kong could be the result of some protective biological and cultural factors.

Hsu (1983) found it methodologically impossible to specify a single cause of anorexia nervosa, as the disorder was probably multifactorial in origin. Among the predisposing factors, obesity and the desirability of slimness, pubertal stress, and issues of dependence versus autonomy have come out repeatedly and prominently. It is in these areas that cultural differences arise.

Most Chinese girls in Hong Kong are slim if not underweight by Western standards. (A comparison of even the ideal weight charts showed more than 5% difference between Chinese and Western girls of the same height.) While borderline anorectic shapes are often rated as highly attractive in the West (Furnham & Alibhai, 1983), it is less easy to imagine that the average Chinese girl can still remain so after some 25% loss of weight. In fact, as in the case of diagnosing prepubertal anorectic children (Irwin, 1981), the 25% criteria in DSM-III (this is changed to 15% below expected body weight in DSM-III-R) may have to be revised in Chinese girls, who have a smaller percentage of total body fat. At the 'threshold weight' of about 42 kg (Crisp, 1980), a significant number of girls are menstruating normally, even when the height difference is taken into account. There is little stigmatisation of the obese (except in the extreme) as having physical, mental, or moral impairment; popular Chinese beliefs are that "being able to eat is to have luck", "gaining weight means good fortune", and "fat people have more luck". Some cultures value obesity as a symbol of success and economic security (Powers, 1980). The desirability and pursuit of slimness, which in the West has been equated with self-control, elegance, social attractiveness, and youth (Dally & Gomez, 1980), are less intense in Hong Kong. Cross-cultural differences in the perception of female body shapes have been studied by Furnham & Alibhai (1983), who showed that despite exposure to Western preferences, Kenyans continued to rate larger figures more favourably and smaller figures less favourably than the British. It thus seems possible that Chinese girls may diet less and have a reduced disturbance of body image, which has been demonstrated in both anorectic and non-anorectic Western girls (Hsu, 1982) and believed to contribute to the development and maintenance of the disorder.

Crisp (1980) believed that puberty assumed a "pivotal" role in the anorectic process, and that its physical changes and psychological demands were vital predisposing factors. Later and less obvious changes of puberty and reduced body fat have been cited as reasons for the much lower incidence of anorexia nervosa in males (Dally & Gomez, 1980). As a general trend, puberty occurs later in Chinese in Hong Kong compared with Western countries, so that the above pathogenetic factors would not exert such a powerful straining effect on a yet developing and immature personality. Besides, the physical changes of contour such as breast enlargement are much less marked for Chinese girls. This would understandably cause less embarrassment, especially for girls in pathological families where competition with the mother's adult figure could be relevant (Crisp, 1980).

Difficulty in gaining autonomy from rigid and restricting parents has been repeatedly incriminated in the Western literature (Bruch, 1978; Garfinkel & Garner, 1982). The Western preoccupation with individual freedom has always stood in contrast to the Chinese concern for social order (Bond & Hwang, 1986). From tradition, Chinese parents have through harsh and protective upbringing moulded their children to exhibit obedience and proper conduct (Ho, 1986). Young people have been described to have a 'delayed' adolescence that could extend well into the late 20s or more. Problems of 'separation from mother' are not evident. The family is expected to function as a cohesive unit in which members are closely interdependent on one another, with potential enmeshment and failure of conflict resolution (Minuchin *et al*, 1978). The father is often rigid and distant (Ho, 1986), another reported pathogenetic factor in Western anorectic families (Crisp, 1980). With all these cultural differences in mind, it has to be concluded that a Chinese family would need to be very restricting indeed in order to contribute significantly to the development of anorexia nervosa, as in case 1 where the parents and family atmosphere were abnormal even by local standards. In fact, the actual interactions could have been under-reported by the parents, a possibility that was well illustrated in a case report (Rampling, 1980).

Hong Kong thus represents a dynamic balance of risk and protective factors. It is tempting but not entirely justifiable to assume that Hong Kong is destined to have a high future incidence of the disorder, as its Westernisation continues. Buchan & Gregory (1984) felt that family interactions were not specific for anorexia nervosa, but exposure to Western social norms were. In Hong Kong the increasing appearance of Western fast-food restaurants may indicate that Western foods (with their generally higher fat, and sugar, and lower fibre content) will be incorporated into the Chinese diet through a gradual process of acculturation. This may create more obesity and concern with weight, and hence eating disorders in our future generations. In Hong Kong health clubs and aerobic classes have started to emerge in recent years, but we do not yet have obesity clinics or the media popularising anorexia nervosa, and certainly not reports of celebrities afflicted with it. Lack of education and awareness about anorexia nervosa can act like a double-edged sword: while leading to underestimation, it can also reduce the likelihood of psychosomatically vulnerable individuals to choose anorexia nervosa as a convenient form of illness. Anorexia nervosa was at one time thought to be a hysterical condition (Lasègue, 1873), and a hysterical epidemic frequently requires a certain threshold beyond which a little epidemiogenic trigger would exert an explosive effective (Benaim *et al*, 1973; Merskey, 1979). But it is our belief that anorexia nervosa, while becoming more common in Hong Kong, is not likely to reach Western proportions. It remains to be seen.

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'Asneezia' – Some Further Observations

G. D. SHUKLA

Absence of sneezing or inability to sneeze was found in 2.6% of psychiatric patients, although only half complained of the symptom spontaneously. This was the most frequent of a triad of features, the others being infrequent attacks, of coryza and light-headedness. Endogenous depression was the commonest psychiatric diagnosis, followed by schizophrenia, but 'asneezics' differed significantly from controls in their diagnostic distribution; they also tended to be older, poorer, and less educated. The course and outcome of the asneezic triad ran almost parallel to those of the primary psychiatric illness.

'Asneezia', signifying absence of sneezing or inability to sneeze, was described by the author as a hitherto unrecognised psychiatric symptom (Shukla, 1985) with slightly over 1% of patients spontaneously complaining of asneezia, which was a prominent symptom. These patients tended to be older, poorer, and poorly educated. This communication presents some further observations on a larger group of patients.

Method

Of 6286 new patients attending the psychiatric services of MLB Medical College, Jhansi, India, over 1984–86, 80 (1.3%) spontaneously complained of 'asneezia'. The remaining patients were asked specifically about the symptom, and a further 86 (1.4%) admitted to having it. Relatives confirmed the absolute absence of sneezing and a total inability to sneeze. In fact, most of them had unsuccessfully tried to induce sneezing by poking their nostrils with wicks or by sniffing tobacco, ammonia, or even chilli powder. Inability to sneeze was verified objectively by making subjects sniff a pinch of snuff. This produced a series of explosive sneezes in the controls (see below) but none in the patients complaining of asneezia.

One hundred and sixty-six controls were selected randomly from among the remaining newly admitted patients and along with the 'asneezia' subjects were subjected to detailed history taking and psychiatric examination. Patients were given appropriate treatment for their psychiatric condition and were followed up to assess the effect of a change in mental condition on asneezia.

Results

The frequency of 'asneezics' among the total psychiatric cases more than doubled to 2.6% when all the patients were asked specifically about the presence of the symptom; 86 patients admitted to having it besides the 80 who spontaneously complained of it. The former did not volunteer the symptom because they did not think it worth mentioning (37 patients) or because the symptom had been ignored or even ridiculed by previous physicians (49 patients).

TABLE I
Diagnostic analysis of asneezics and controls

Diagnosis	*Asneezics*		*Controls*	
	n	%	n	%
Schizophrenia	59	35.6	51	30.7
Endogenous depression	70	42.2	24	14.5
Neurotic depression	20	12.1	21	12.6
Hypochondriasis	17	10.2	5	3.0
Others	—	—	65	39.2

Asneeziacs v. controls: $\chi^2 = 55.4$; d.f. $= 3$; $P < 0.001$.

The socio-demographic characteristics of the patients were similar to those described earlier (Shukla, 1985); they were older ($t = 5.15$; $P < 0.001$), poorer ($\chi^2 = 6.2$; $P < 0.05$) and less educated ($\chi^2 = 11.4$; $P < 0.01$) compared with the controls. There was a slight female preponderance among the asneezics, while the controls had a male proportion ($\chi^2 = 2.69$; $P > 0.10$). Diagnostic analysis revealed significant differences between the two groups ($\chi^2 = 55.4$; $P < 0.001$) (Table I). Since the diagnostic difference between the two groups was largely because of endogenous depression the condition is further elaborated in Table II.

Phenomenologically, asneezia was found to be frequently associated with two other related symptoms, namely

TABLE II
Diagnostic breakdown of patients with endogenous depression

	Asneezics		*Controls*	
	n	%	n	%
Involutional depression	45	64.3	7	29.2
Depressive phase of bipolar affective psychosis	12	17.1	10	41.7
Unipolar affective psychosis	8	11.4	5	20.8
First attack of depression at an early age	5	7.2	2	8.3
Totals	70	100.0	24	100.0

Patients v. controls: $\chi^2 = 9.5$; d.f. $= 2$; $P < 0.01$.

infrequent or no attack of coryza (80.7%) and a feeling of light-headedness (69.8%). These three symptoms formed a well defined constellation (the 'asneezic triad'), which cut across all four diagnostic groups.

Response to treatment

Of the 59 schizophrenics with asneezia, 48 had a good response to treatment with antipsychotics and/or ECT, six had slight or no change, and the remaining five could not be followed up. In all but four of the 48 patients who responded well, sneezing reappeared, but asneezia persisted in all six patients with slight or no improvement. Of the 70 patients with endogenous depression, 61 responded well and recovered completely from both depression and asneezia with antidepressants and/or ECT. The remaining nine patients were lost to follow-up. Nine of the 20 patients with neurotic depression and 11 out of 17 with hypochondriasis continued to have asneezia as well as psychiatric symptoms, despite treatment with antidepressants and psychotherapy. In the remaining 11 and 6 patients respectively, sneezing returned, even though some psychiatric symptoms persisted.

Discussion

After the publication of the earlier paper on asneezia (Shukla, 1985), the author received various communications regarding the symptom. Van Dijk (personal communication) reported: "to my experience, the described symptom does not appear 'peculiar to patients from India and perhaps other developing countries', but it manifested itself in my practice also". He then described a 47-year-old single man who was very upset because he could not sneeze and had become "demoralized after his own unsuccessful measures like looking into the sun and sniffing salt". He was diagnosed as having a schizoid (schizotypal) personality disorder with a depressive reaction, and with improvement of the general psychiatric condition, sneezing returned. The patient was poorly educated and came from a lower socio-economic background.

Pfeiffer & Aston (1982) observed that the "Schizophrenic patient seldom has inhalant allergies and therefore seldom sneezes [even] during the hay fever season". They tried to test the sneeze reflex of schizophrenics with the help of a strong sternutator, but had to abandon this on finding that they could not tolerate the slightly open bottle at arm's length under the patient's nose: "We all had fits of sneezing while the patient continued to mumble incoherently. . . . Obviously, some mediator of the body's sneeze reflex must be in low supply – perhaps histamine could be low". These authors found schizophrenics to have low blood levels of histamine, which rose to normal on treatment with an antipsychotic drug. This is in keeping with the observations of Lehmann (1980) and Verghese (1984) that schizophrenics suffer less frequently from various allergies and are resistant to relatively high doses of histamine.

Clark (1986) doubted the genuineness of 'asneezia'. Reacting to Shukla (1985), he considered that, in view of the importance of sneezing in the Indian culture and the poor educational and socio-economic background of asneezics, the author was "reporting culturally determined hypochondriacal over valued or delusional ideas". Such ideas, Clark says, occur in up to a fifth of schizophrenics and are well known in affective disorders, and these disorders constituted the majority of the asneezics. However, in view of the fact that the symptom has been found in such diverse cultures as those of India, Holland, and the United States, it can no longer be said to be culture specific. Further, the absence of sneezing in these patients has been objectively verified by Pfeiffer & Aston (1982) and the present author, thereby leaving no doubt as to the genuineness of the symptom.

Both the earlier (Shukla, 1985) and the present studies have shown asneezia to be associated more with endogenous depression, particularly of the involutional type, than with schizophrenia. Could it therefore be somehow related to the agitation and restlessness which are virtually universal in involutional depression and are also seen in a quite substantial proportion of schizophrenics, neurotic depressives, and hypochondriacs (Slater & Roth, 1986)? Is the relationship biochemical, immunological, behavioural, or a combination of all these and some other hitherto unrecognised factors? How do we account for the socio-economic and educational background of the 'asneezics'? There is a need to elucidate the pathophysiological basis of asneezia by well planned intensive studies.

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Case Conference

Thirty Years' War: A Battle with Insomnia

J. R. NEWTON, C. SHAPIRO and A. STEWART

A 72-year-old man with a 30-year complaint of intractable insomnia had a positive family history of depression. He first came to psychiatric attention in 1958, after attacking his wife. He was prescribed barbiturates, and later was given meprobamate and nitrazepam, but with no effect on his complaint. The patient tended to increase the dosage of any drug given, of his own accord. EEG sleep recording confirmed the diagnosis of nocturnal myoclonus. It was hoped that at the case conference further treatment stratagems would be suggested.

Objectives

There has been much interest over recent years as to the cause and management of insomnia, although it is rarely the presenting complaint. In this case the patient complained bitterly of insomnia and believed that it was his only problem. In presenting this case, we hoped there would be discussion about diagnosis, the place of benzodiazepines in this patient's treatment (which had been problematic), and that alternative treatment strategies might be suggested. The conference lasted 55 minutes.

Presentation of case by Dr Newton

The patient

Mr X, a 72-year-old retired police sergeant, had been attending the Psychiatric Day Hospital at the Royal Victoria Hospital, Edinburgh, each week since 1982. Over this time his main complaints had been insomnia, anxiety, and low mood. He lived with his wife in his own house, was a non-smoker and took alcohol only occasionally. He had no outside social activities, and complained of having no energy to attempt any jobs around the house. His pre-morbid personality was described as serious-minded, tending to pessimism.

He complained of:

(a) absolute insomnia for nine weeks, associated with low mood, drowsiness during the day and a feeling of lack of energy

(b) feelings of his right foot "beating" all day and night – at times he said this was the only sensation he had ever had; however, he also described a stretching sensation in his right leg, beginning a few minutes after going to bed.

Family history

His father, a retired depot foreman, died at the age of 84 years of a cerebrovascular accident. The patient had a good relationship with his father, but had been closer to his mother, who died at the age of 54 of a myocardial infarction. He described his mother as a "worrier". She had a history of recurrent depressive illness, for which she was treated at Rosslynlee Hospital as an in-patient. The patient identified strongly with her history of psychiatric illness.

He had a sister, two years younger, with whom he got on well, and who also complained of insomnia. She was single and had a history of depressive illness, treated at the Royal Edinburgh Hospital. The patient also had a brother ten years younger, with whom he had little contact, but claimed they got on well. The brother's son had recently died and the brother was then treated for a depressive illness, but had no previous psychiatric history. The patient also had a maternal uncle, who had received treatment in Craighouse Psychiatric Hospital for depression.

Personal history

Mr X was born in 1915, near Biggar. He had a normal birth and a happy childhood, and several friends. He frequently walked in his sleep. He went to school between the ages of 5 and 15 years, changing school aged 13 years after a family move. He was average academically, but enjoyed neither work nor sports.

He knew his wife for five years before their marriage in 1942. Their marriage has always been difficult, she being a somewhat extroverted person who enjoyed socialising. For most of his working life they led separate lives. In 1958, Mr X attacked his wife and was charged with attempted murder. This charge was dropped, although his wife still believed that he meant to kill her. This attack precipitated his first contact with the psychiatric services (see below).

It appeared that the couple's sexual life had always been unsatisfactory; his wife claimed that their marriage was not consummated, although earlier histories do suggest that initially they did make love. Any sexual activity stopped in 1958. They now slept in separate rooms. They had no children because, Mr X suggested, they felt their financial situation did not allow it.

Mrs X had extramarital affairs, with Mr X's knowledge. She still pursued a social life separate from him. Neither of them found it easy to talk about their marriage: Mr X denied any marital difficulties and, up until two years previously, refused to allow staff to contact his wife. The couple communicated little, although Mrs X was concerned about her husband, and frequently telephoned or came to the day hospital to talk about him.

Occupational history

Mr X worked for seven years as a council labourer. He did not enjoy this and felt he was not using his abilities fully. He spent one year as a van driver and then seven years as a quarry blaster, and was then exempt from call-up during the war. In all his placements he had a good relationship with his workmates. In 1945 he joined the police force, until retirement in 1980; he did not find the job satisfying, but was pleased when he was promoted. He worked shifts but did not object to the antisocial hours.

Medical history

The only relevant past medical history is that Mr X had a motorbike accident when aged 16 years, and was admitted to the Royal Infirmary of Edinburgh. He was treated for post-traumatic amnesia for three days.

Psychiatric history

In 1958 Mr X began to sleep badly, with low mood and irritability. While out in the garden one day, his wife was nagging him and he hit her, causing her to fall over. This had never happened previously, and she was terrified. A charge of attempted murder was dropped, but it was recommended that he see a psychiatrist. A diagnosis of depressive illness was made, and he was treated with ECT, making a good recovery. He was discharged on barbiturate medication for his poor sleep.

In 1964 he had recurrence of depressive illness and was treated at the Royal Edinburgh Hospital as an out-patient with ECT (for which no notes are available). On this occasion his mood improved, but he continued to complain of poor sleep.

In 1978 he was treated for a further relapse of depressive illness as an out-patient. This time he was placed on amitriptyline, but again his complaint of insomnia continued.

He was referred to the Royal Victoria Hospital Psychogeriatric Department in 1981 with complaints of depression and insomnia. At that time he was taking meprobamate (400 mg *nocte*) and amitriptyline (25 mg *nocte*). He was seen by a psychologist, who felt that he would be best treated by being encouraged to find new interests in his retirement and encouraged to undertake graded activity. Initially, he responded well to this.

He was re-referred in 1982 with complaints of poor sleep and "churning" in the stomach. Nitrazepam (10 mg) had then been substituted for amitriptyline. A diagnosis of agitated depression was made and he was treated with doxepin (75 mg daily). In addition he complained of forgetfulness and it was felt that he may have had an early dementia. Treatment at the day hospital improved his mood, but his complaints of insomnia persisted. Continued attendance at the day hospital was recommended but attempts to withdraw him from meprobamate (800 mg) and nitrazepam failed.

In 1984 his wife noted that his ability to cross the road was poor and that he had poor self-care. She blamed this on his medication, which was then amitriptyline (150 mg *nocte*), meprobamate (1200 mg *nocte*) and nitrazepam (10 mg *nocte*). His own complaints were of insomnia, "churning" in his stomach, and "twitching" in his legs at night. It was noted, however, that he actually slept approximately eight hours a night.

In December 1985 cognitive testing was again carried out and showed deficits in psychomotor speed, and visual and verbal memory. It was felt that this may not have reflected any organic deficit, but rather the effects of long-term psychotropic medication.

In March 1986 he was withdrawn from meprobamate. He continued on amitriptyline (200 mg *nocte*) and nitrazepam (10 mg *nocte*). He continued to complain of poor sleep associated with restlessness in his legs at night. His memory impairment improved slightly. Computerised tomography (CT) of the brain was normal.

In September 1986 he was admitted to the Royal Victoria Hospital with complaints of low mood, agitation, insomnia and an uncomfortable stretching sensation in his legs associated with a feeling that when sitting, his feet were gripping the carpet. It became apparent that his insomnia worried his wife as she feared he might strangle her in her sleep, and she felt that she could only sleep safely when he was asleep. All attempts to arrange marital counselling had failed. Initially a diagnosis of anxiety state, secondary to tranquilliser withdrawal was made and he was started on a trial of chlorpromazine. His mood became much lower and he insisted that he could be helped only by ECT. After a month's trial of trimipramine (150 mg), ECT was commenced, and after five treatments his mood, sleep, and the stretching sensation in his legs had improved. Before discharge in November 1986 he was noted to have developed a right foot drop due to peroneal nerve damage secondary to pressure effects. This gradually resolved. Discharge medication was trazodone (100 mg *nocte*). Two weeks later he was again complaining of insomnia and he had increased his trazodone to 300 mg *nocte*. He again requested a further course of ECT.

In January 1987 mianserin was substituted for tradozone and pericyazine also started. He increased this to mianserin (180 mg *nocte*), and continued to self-medicate with some left-over trimipramine. At that time he was also taking pericyazine (10 mg daily). After a short respite in July 1987, he continued to complain bitterly of insomnia and stretching sensations in his legs, but nursing staff noted that he did sleep all night. In September 1987 all medication was stopped, with initial improvement in his symptoms. However, all these symptoms had now returned.

Mental state examination

Mr X was a neat, tidily dressed man with good eye contact, who tended to become slightly agitated when discussing his insomnia. His speech was normal in tempo and form, but the content centred around his insomnia. He had reduced emotional reactivity, but no subjective complaints of low mood. He had no delusions, hallucinations, experiences of depersonalisation, or obsessional phenomena, and was fully orientated in time, place, and person. He had good concentration and attention, and a good knowledge of current affairs, but made three mistakes on recalling a name and address with six parts after two minutes, and four after five minutes, and had difficulty in remembering sequences of events and dates in his personal life. He believed that his illness was inherited from his mother and that the insomnia was caused by working shifts. He strongly believed that a sleeping tablet would cure him.

Physical examination

On physical examination, no abnormalities were detected and laboratory results were all normal.

Presentation of case by Sister Clancy

Mr X attended the Royal Victoria Day Hospital for psychiatric care since 6 November 1982, and I have known him for all of this time except for an in-patient assessment period from September to November 1986.

Referral to the service was with a diagnosis of: (a) flatness of affect, and (b) insomnia.

Mr X attended one day a week using public transport. At that time he was attending a local day centre for a woodwork class which he did not care for and which he later stopped.

His appearance was of a well built, healthy looking man, weighing 90 kg. His dress was smart but casual. His day hospital attendance has been very regular, although home reports of his staying in bed all day or never getting dressed were passed to us by his wife. She added that he had very little conversation with her.

He was not a mixer at the day hospital and currently he attended one day per week. He refused to attend group work. He sat looking withdrawn, occasionally nodding off to sleep. Sleep hygiene has been a repeated topic of discussion but to no avail. During the present time of investigation, Mr X was showing some hope that a treatment was available to cure his insomnia. This was his usual response to a change in treatment. At a later date he became friendly with a young female arts graduate, who was working as an auxiliary. He would call her at the art firm where she was later employed. Mr X would regularly ask to see the doctor as "the tablets were not working". He complained of depression and of being unable to sleep. He would frequently insist that this was a hangover from his shift work. His drug compliance was irregular and the fact of his taking extra tablets was noted. His arrival and departure times from the day hospital never varied.

During 1983 he took part in group work, which looked at feelings and the sharing of treasured possessions. His verbal interaction was low. However, he did bring small family antiques to the meetings in common with the other group members.

His wife reported his memory loss. She asked for the ambulance service to bring her husband for day care in case he lost his way using the buses, but he refused to comply.

On return to day care in November 1986 he exhibited some change. He had lost 10 kg and was less motivated. He used the ambulance service and attendance days were increased to three per week. However, he refused to continue with this, saying he did not have the energy to attend so often.

Both Mr X and his wife have made demands on the team. At times she arrived without an appointment and expected immediate and effective action.

A written contract was drawn up which was signed on 12 June 1987. Mr X had:

(a) to realise that the doctor had 49 other day-care cases and he was to consider carefully before asking to see medical staff
(b) to understand that unit medical staff were not to be contacted, except on scheduled days of attendance
(c) to agree to comply with treatment for the specified time
(d) to agree not to adjust doses of tablets
(e) to go outside at least once a day
(f) to take and collect his own prescriptions from the chemist and not ask his wife to do this.

This plan was not successful.

Since all medication stopped in September 1987 for the first time he was more alert, brighter in mood, and less complaining.

Questions

DR ADAMS *(senior registrar)*: What evidence was there that the patient was or was not sleeping? Had you performed a sleep EEG?

DR STEWART *(consultant in charge of case)*: We will discuss the EEG reports later. The nurses noted that he did sleep most of the night when on the ward. Occasionally Mr X did have a disturbed night, sitting with his leg hanging over the side of his bed.

DR GASKELL *(senior registrar)*: What did Mrs X come up to ask the day hospital staff?

SISTER CLANCY: She came up to talk about his insomnia and what we were doing about it.

DR PARRY *(consultant)*: Is the patient off all medication now?

DR STEWART: Yes.

PROF. OSWALD *(special interest in sleep disorders)*: Why not leave this man on the drugs for which he is clamouring?

DR STEWART: Weaning him off the drugs may improve the level of function. In this man, too, there is always the danger that he will abuse whatever drugs he is given. This patient has a history of violence and giving him benzodiazepine may have a disinhibiting effect on his behaviour.

PROF. OSWALD: Having had the opportunity to read the notes, I know that up until 1982 his wife went dancing with an 83-year-old man every Saturday night and that also Mr X went out every Saturday night. Has this been discussed with the patient?

DR STEWART: Mr X would not discuss his own activities on Saturday nights. Up until two years ago, Mr X refused to let us contact his wife. He and his wife lead separate lives.

PROF. OSWALD: In 1958 he had a diagnosis of depression and a murder charge against his wife was dropped. Is it possible that this was due to her involvement with lovers? It was also then that according to the Royal Edinburgh notes he started barbiturates.

DR STEWART: This is not known.

Interview

Mr and Mrs X were introduced to Professor Oswald. Mr X was wrapped in coat, scarf and hat (on a moderately warm day), and made few expressive gestures throughout the interview, paying no attention to the presence of an audience. Mrs X, a sprightly lady, heavily made up, and wearing fashionable dress and hat, smiled brightly to the audience, greeting people she recognised. She often answered questions directed to her husband, and answered all questions addressed to them as a couple.

PROF. OSWALD: Thank you for coming and facing such a formidable audience. We've heard that you've been ill for many years. (Assent.) How long have you been retired?

MR X: When I was 65.

PROF. OSWALD: What year was that?

MR X: Seven years ago.

MRS X: He retired 2 October seven years ago. He has been retired seven years now because he retired 2 October seven years ago.

PROF. OSWALD: What year was that?

MRS X: Seven years ago.

PROF. OSWALD: What problems do you have now?

MR X: I am not sleeping.

PROF. OSWALD: Do you have any other problems?

MR X: I am not sleeping.

PROF. OSWALD: What ill effects do you notice?

MR X: It is the worst thing that could happen to anyone.

PROF. OSWALD: Why is that?

MR X: Because it gives you energy.

PROF. OSWALD: If you don't sleep at all all night, do you get drowsy during the day?

MR X: No.

PROF. OSWALD: How many years have you had this problem?

MR X: I have not slept at all for the past ten years.

PROF. OSWALD: From the notes, I understand it was six years ago that the sleep trouble started.

MR X: No, it was five years ago.

PROF. OSWALD: I understand that you have been taking sleeping tablets since 1958.

MR X: No, they were antidepressants.

PROF. OSWALD: Had you been taking barbiturates?

MR X: No, I took Equanil [meprobamate]. I took it during the day to help me sleep as I was doing night-shift work.

PROF. OSWALD: We know that you have some difficulty with your memory. (Assent.) Can you remember when the stretching in the legs started?

MR X: It's quiet at night.

MRS X: The stretching started after he had the ECT.

PROF. OSWALD: When was that?

DR STEWART: In November 1986.

PROF. OSWALD: Did you get it before then?

MR X: No.

DR STEWART: The first record in our notes is 1984.

PROF. OSWALD: If you sleep in separate rooms, how do you know that your husband isn't sleeping?

MRS X: Sometimes I've seen him at night – I've told you, Dr Stewart – and he's shouting and screaming with the pain.

PROF. OSWALD: From the case notes we see that you used to go dancing on Saturday night. Do you still enjoy that?

MRS X: No, not for the last year. I can't leave him. We've known the man I went with for many years. He's an old friend of ours. He's much older now, but he still comes round to visit us.

PROF. OSWALD: And where did *you* go?

MR X: Nowhere, I don't go out. Maybe for a drink.

MRS X: He doesn't like company.

PROF. OSWALD: If your sleep was perfect, would you be happy?

MR X: I don't sleep at all. If I did, I would be, yes.

PROF. OSWALD: From the case notes it would seem that you do sleep.

MR X: I don't sleep at all.

MRS X: After he gets up in the mornings, he has his breakfast and then goes back to bed. After lunch he just sits in the sittingroom all day doing nothing.

PROF. OSWALD: Do you mind if anyone else from the audience asks you questions?

MR and MRS X: No.

DR PARRY: Mr X, you don't sleep at all at night. Can you relax when you are in bed?

MR X: No, it's on my mind all the time.

DR PARRY: If it were out of your mind, would you be able to relax?

MR X: Yes.

DR PARRY: Would you describe your life as lonely? (Assent.) Do you have any friends?

MR X: Yes, my sister.

DR PARRY: Do you have any close friends of your own sex?

MR X: No.

PROF. OSWALD: Why can't you sleep?

MR X: I don't know.

PROF. OSWALD: How does it affect you?

MRS X: Well, I worry about it.

PROF. OSWALD: Why is that?

MRS X: Well because of what happened before.

PROF. OSWALD: What do you mean?

MRS X: Because of what happened in 1958 – you know – with him.

PROF. OSWALD: Could you tell us about that?

MRS X: Well, he wasn't well you know.

PROF. OSWALD: In 1958?

MRS X: Yes.

PROF. OSWALD: Could you tell us more?

MRS X: He was tending a field behind our house. I saw him and his eyes were red and he was foaming at the mouth. . . .

PROF. OSWALD: Were there any reasons why Mr L should be angry with you then?

MRS X: No.

PROF. OSWALD: How were you getting on?

MRS X: We were getting on well.

PROF. OSWALD: There weren't any tensions between you?

MRS X: No.

MR X: [At the door, leaving with his wife, to Professor Oswald]: You must have a sleeping tablet for me.

PROF. OSWALD: Well, there are many types, but we have to weigh up the benefits of them against the risks.

MR X: But you must be able to give me something.
PROF. OSWALD: Well, that is something to discuss with Dr Stewart later.
Meanwhile Mrs X gathered up her coat and hat and left with a smile and a gracious wave to the audience.

Further reports

A sleep laboratory study showed nocturnal myoclonus (paroxysmal leg movements of sleep) with sleep disturbed by five episodes of prolonged wakefulness. A short video of the sleep study showed both legs jerking abnormally while Mr X was asleep. The video also showed an interview with the patient and his wife after they had seen both the sleep record and the video evidence of Mr X sleeping. Mr X refused to believe this evidence and insisted that he never slept.

Conference discussion

PROF. OSWALD: With the information we have, there is the possibility of multiple diagnosis. Would anyone like to comment?

MRS GILLIES *(principal hospital pharmacist)*: How long did it take to withdraw him from the meprobamate?

DR STEWART: Approximately three or four months.

MRS GILLIES: Over six months would be best. With abrupt withdrawal one can get twitching.

DR MCINNES *(clinical neurophysiologist)*: One doesn't get that sort of muscle twitching with meprobamate withdrawal.

PROF. OSWALD: Let us start at the easy end, with the legs. Dr Keyhoe, would you like to comment on these legs?

DR KEYHOE *(registrar)*: What I would like to ask is, haven't doctors been colluding with this man by giving him medicines if, in fact, he has been sleeping?

DR STEWART: Yes they have colluded with this man. He refused to contemplate coming off the drug which he received from his GP who was also very concerned about their continued use.

DR MORRIS *(registrar)*: Would it be justifiable to give this man a placebo instead of a sleeping tablet?

DR STEWART: We gave him calcium lactate about three years ago. It made him constipated and he refused to continue with it.

DR REHMAN *(registrar)*: Was there any epileptic activity on the man's EEG?

DR SHAPIRO: No.

DR MCINNES: What he was also complaining of were unpleasant sensations in his legs during sleep. Clonazepam is suggested for restless legs, but it may not stop the movements, only reduce the subjective awareness of them.

DR CHICK *(consultant)*: I have come across such symptoms in people taking mianserin. They should be recognised as important symptoms in anyone complaining of insomnia.

DR MCINNES: There is no objective evidence of him having myclonus at rest when awake.

There was then some discussion about the association between nocturnal myoclonus and restless legs. Dr Shapiro produced a slide which showed that restless legs were often associated with nocturnal myoclonus (Table I).

TABLE I
Restless legs and sleep myoclonus

	Restless legs	*Sleep myoclonus (periodic movements during sleep, PMS)*
Time of occurrence	Wakefulness, evening early sleep	Sleep
Sleep stage	Non-REM 1 and 2	Non-REM sleep (inhibited during REM sleep)
Sensory component	Present	Absent
Character	Restless, not myoclonic	Periodic jerks
Distribution	Generalised, both legs	Tibialis anterior
Association	Anaemia, gastrectomy, sensory neuropathy, nerve damage, uraemia	Occult, but occurs in narcolepsy, sleep apnoea
Concurrence	Usually associated with sleep myoclonus	A third of cases associated with restless legs
Presenting complaint	Extreme sensory discomfort	No symptoms: sometimes insomnia or daytime drowsiness
Treatment	None very effective, sedatives	Uncertain: clonazepam and other benzodiazepines may reduce awareness of jerking

After Parkes (1985) (with permission).

PROF. OSWALD: What are we going to do with this chap? Dr Stewart will not give him the drug he so desires.

DR GASKELL *(senior registrar)*: It is an impossible problem. The major problem is their relationship, and you cannot treat the insomnia without treating the relationship.

DR STEWART: We tried to introduce marital therapy but Mr X would not co-operate.

PROF. OSWALD: This man has had 30 years of being thought of as having medical problems. Could all these doctors have been wrong?

DR PARRY: If you put him on medication, he will still complain of his symptoms. I would have liked the Professor of Psychiatry at Edinburgh University to have told this man "There is no drug".

PROF. OSWALD: I am an honest man.

DR SERFATY *(SHO)*: If you do not give him some medication to relieve his distress, is it not likely that he will use some other form of relief such as alcohol abuse?

DR PARRY: Well, he hasn't so far, so that may not happen.

PROF. OSWALD: Dr Jacques, you are a psychogeriatrician, what are your thoughts? Would you treat this man?

DR JACQUES *(psychogeriatrician)*: This man is very determined to be given sleeping tablets. You appear to have entered into a little battle with him. Most of the doctors over the 30 years have probably been wrong. However, he is determined to win and I think in this case discretion is the better part of valour.

PROF. OSWALD: We do not know everything. The pendulum has swung against the benzodiazepines everyone used at one point. We now feel that people should be encouraged to recognise that sometimes sleep isn't as good as it may have been in their past. What is the value of making a diagnosis of myoclonus and restless legs?

In the late '60s funding was withdrawn from the sleep labs in the USA, and because of this the sleep researchers had to find alternative funds from people with insomnia and money. They would pay for such diagnosis made, with the more electrodes sticking into them the better. [Oswald (1981)]

But Kales at Hershey (1982) studied 200 insomniacs and controls, and discovered that the two groups had the same incidence of nocturnal myoclonus. These people often have bitter complaints of not sleeping, even though they do sleep, and treatment will probably not change that.

Conclusions

The discussion ended without any firm conclusions being drawn. The following diagnoses were made: (a) restless legs syndrome; (b) nocturnal myoclonus; (c) drug dependency; (d) early dementia. Current active problems were considered to be: (a) insomnia; (b) lack of volition and energy; (c) lack of social activities; (d) susceptibility to toxic drugs and side-effects of psychotropic drugs; (e) marital problems.

It was felt that there was no agreement at the conference on whether benzodiazepines should be used in this case. The presenting team felt that this man represented a high risk for abuse and dependency on such medication, and we felt that any treatment should be non-addictive and relatively non-toxic. Many drugs have been suggested as useful in the treatment of restless legs syndrome, clonazepam (Oshtory & Vijayan, (1980), carbamazepine (Telstad *et al*, 1984), propranolol in patients who have received neuroleptics (Lipinski *et al*, 1983), 5-hydroxytryptophan (Billiard *et al*, 1978), and opiates (Trzepacz *et al*, 1984). As a result of the case conference it was decided that L-tryptophan was the most appropriate drug for Mr X, and he was commenced on 2 g *nocte* with the intention of increasing this over a month to a maximum of 6 g *nocte*, and to evaluate the response after a one-month trial.

Theoretical note

It is interesting that the patient's sister also complained of insomnia and sensations in her legs in the evenings. Several authors have suggested that familial restless legs (see Parkes, 1985) may be transmitted through an autosomal dominant gene. Onset in such familial cases is usually in the second decade of life.

Weschler *et al* (1986) suggested that abnormal blink reflexes may occur in all patients with periodic leg movement in sleep. Although this patient had confirmed periodic leg movement in sleep, blink reflexes were normal.

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Point of View

The Damnation of Benzodiazepines

F. KRÄUPL TAYLOR

It is argued that there are two kinds of benzodiazepine dependence: a therapeutic and a morbid kind. The therapeutic dependence is acceptable in that it mitigates the clinical manifestations in patients with long-standing and fluctuating anxious-depressive symptoms. The morbid dependence is an unfortunate complication which can arouse therapeutic concern because it ties patients to an excessive dosage, unless the penalty of a sometimes grim abstinence syndrome is paid on drug reduction. The present, often strident and threatening, damnation of benzodiazepines oversteps the mark and causes avoidable misery to patients whose well-being has become largely and therapeutically dependent on the drug.

In the 1960s, benzodiazepines became available for the treatment of patients with anxiety, sleep disturbance, muscular spasms, and epilepsy. They began to replace barbiturates, which until then had had pride of place in this respect. Benzodiazepines were of equally high therapeutic efficacy, seemed to have few side-effects and, above all, were safe, since overdoses were hardly ever fatal. Oswald (1983), for example, reported that "in the Edinburgh Poisons Unit, having some 2000 admissions per year, the number of unconscious patients admitted had steadily declined year by year since the benzodiazepines came increasingly to be taken, and deaths as a consequence of benzodiazepines are rare".

No wonder that the number of prescriptions for benzodiazepines gradually rose to unexpected heights. Yet this very rise began to undermine their therapeutic popularity. Warning voices started to be heard. The damnation of benzodiazepines was on its way. It was maintained that society was becoming overmedicated; that people, instead of stoutly tackling the vicissitudes of life, recoiled from them with the help of tranquillising drugs; that doctors were too ready to provide a pill for every ill, thus avoiding the more onerous task of helping their patients to come to grips with problems that could be solved or ameliorated.

Psychiatrists were among the first who tried to stem the tide of benzodiazepine prescriptions, warning that benzodiazepines seemed to have become the "opium of the masses" (Lader, 1978). It was generally agreed that doctors should be more careful in prescribing these and other psychotropic drugs, that they should not blindly provide repeat prescriptions for them, but should monitor their patients' medication at relatively short intervals. It also began to be realised that benzodiazepines were often not the best drugs for treating anxious and depressed patients, but that antidepressants (including monoamine oxidase inhibitors) could be superior. Certainly all these considerations had an effect. The number of prescriptions for benzodiazepines began to fall in several countries, including England, in the late 1970s (Marks, 1985*a*). There even emerged voices among the experts which spoke in favour of benzodiazepines. Rickels (1981) remarked:

> "An almost irrational concern with the possible overuse of benzodiazepines can be observed in some who completely disregard the shortcomings of available alternatives – including use of alcohol or marijuana, smoking and overeating – which are certainly much less appealing from the point of view of public health than is the use of benzodiazepines. It should be kept in mind that non-drug psychotherapeutic approaches as alternatives to drugs and support are frequently not available . . . [or] unacceptable alternatives."

Marks (1975*b*) said in a similar vein:

> "There is justification for the argument that the level of use of [benzodiazepines] in women is not too high, but that the level in men is too low. With increased appropriate prescriptions of benzodiazepines, some cases of alcoholism, evolving from self-medication of emotional distress, might be prevented. Also work absenteeism, resulting from significant emotional factors, might be reduced."

Morrison (1974), a Canadian minister of state, when arguing against legally restricting the administration of psychotropic drugs, had this to say:

> "Mental anguish causes at least as much suffering as physical pain and may have somatic consequences. Rational, responsible use of psychotropic drugs to relieve even ill-defined psychological disorder should not be considered as a craven surrender to human weakness. There is nothing really noble about needless suffering."

However, by then the media had joined the chorus of damnation. Their clamour was usually no more than biased and ill-informed sensationalism. Yet the public was now alerted and alarmed. When Manheimer *et al* (1973) examined, in a nationwide survey, what the attitudes and beliefs of American adults were about such minor tranquillisers as benzodiazepines, they found that 87% agreed with the statement: "it is better to use willpower to solve problems than it is to use tranquilizers"; and 40% agreed that "taking tranquilizers is a sign of weakness". Respondents with the least education were the most likely to agree to those two statements. From the values given by the authors, one can calculate that this trend is highly significant statistically ($\chi^2=28.22$ and 51.75, d.f.$=3$, $P<0.0001$).

However, patients on benzodiazepines found themselves at least partially exonerated when it was convincingly shown that, for some of them, willpower was of no avail. Even when they were on a therapeutic dosage, they could no longer free themselves from their medication because, when trying to do so, they were overwhelmed by distressing and even unbearable symptoms. They had become drug dependent in an unpleasant way.

The term drug 'dependence' was introduced by the World Health Organization in 1964 to replace the term 'addiction', which had given rise to confusion because it had been differently understood by physicians, lawyers, and sociologists. It was defined (World Health Organization, 1974) as:

> "a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include compulsion to take the drug on a continuous or a periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence."

The 'compulsion' mentioned in this definition is certainly too strong a word, when the dependence is merely a need to "avoid the discomfort of [a drug's] absence".

The definition of dependence usually incorporates some deficit, but it is an ethical and not a medical deficit because the patients have been enslaved and robbed of their freedom of choice. It has nothing to do with the occurrence of side-effects, which are present with almost all medications. For instance, the insulin-dependent diabetic has side-effects which are clinically more conspicuous and troublesome than those with patients on benzodiazepines, where the detection of side-effects often needs a laboratory toothcomb.

The term 'drug dependence' may conjure up the image of dishevelled, pleasure-craving, doped individuals, leading disreputable lives on the outskirts of society. Yet patients on benzodiazepine medication are quite obviously not of this egregious kind. They lead fairly normal lives, even when they are plagued by anxious-depressive symptoms that are not fully controlled by the drug. They do not frantically search for a drug supply, and hardly any of them develop the sort of drug tolerance that would force them to increase their dosage to an excessive level. Benzodiazepine dependence is thus of a special kind.

To analyse this dependence adequately, it will be helpful to have a suitable conceptual framework. I propose to use the framework I set out in my book *The Concepts of Illness, Disease and Morbus* (Taylor, 1979). It bases itself on logistic theories about sets and classes.

We might start with the statement that any particular class of patients is characterised by a particular kind of morbidity – or, briefly, by a particular 'morbus'. Unfortunately, this is a purely theoretical statement which does not lead us very far. In practice, we deal only with diagnosed patients and diagnosed morbi.

How then do we diagnose morbi? There are several possible and involved answers to this question (e.g. Scadding, 1967; Kendell, 1975). I prefer to be guided by actual usage. In everyday life, a morbus is diagnosed when symptoms are observed in persons that are in some ways abnormal and that call out for some form of treatment. We shall say that such symptoms cause 'therapeutic concern', allowing this term to do duty also for concerns that are diagnostic or prophylactic. These concerns can be aroused in the patients themselves and/or their lay or medical environment. Therapeutic concerns are thus subjective experiences, influenced by individual inclinations as well as cultural trends and fashions. There is nothing definitive and absolute about them. That is why the diagnosis of morbi has undergone so many changes in medical history. There was, for instance, a time – and it lasted two centuries (Hare, 1962; Engelhardt, 1974) – when masturbation was denounced as an evil morbus in need of punitive forms of prevention and treatment. The same could once be said of homosexuality, but today it is a 'psychosexual disorder' only for those "homosexuals for whom changing sexual orientation is a persistent concern" (DSM–III; American Psychiatric Association, 1980), i.e. only when therapeutic concern is aroused in the persons concerned.

Therapeutic concerns evoked in doctors do not, and should not, immediately give rise to therapeutic procedures, unless these are urgently and quickly needed. Before treatment comes the task of establishing what kind of morbus we are dealing with – the task of diagnosis. This is based on the observations made by clinicians, the medical theories they entertain, and the information they can gather from the patient and his environment. In modern times, medical theories have been fashioned by ideas that were originally propounded by Virchow (1858). According to him, the most significant component of a morbus is its cellular pathology and the somatic consequences deriving from it. He attached the name 'disease' firmly to these pathological changes in cells and soma. It became the task of doctors to infer such Virchowian diseases from their clinical observations. Developing Virchow's ideas, Feinstein (1967) has recently suggested that a morbus can be divided into three components.

The first component he called, in agreement with Virchow, a *disease*. But diseases are nowadays no longer exclusively based on a cellular and somatic pathology. Today we also have to take into account molecular pathologies. Indeed, it appears that, for the most part, functional anomalies, including psychological ones, are mediated by abnormal molecular events. When such events are in the foreground, the term 'disorder' is often used instead of 'disease'; and the otherwise outmoded term '(molecular) mechanism' still has its adherents, for example, among psychopharmacologists.

For the second component, Feinstein used the expression *host*. It is meant to refer to the non-diseased part of a patient's body, as well as to his personality and social situation (age, sex, occupation, social status, cultural background and family influences).

The third component is the clinical *illness*, i.e. the symptoms of which the patient and his social environment become aware, as well as the signs which can be elicited clinically and in the laboratory.

We are now in a position to return to our consideration of drug dependence in general, and benzodiazepine dependenc in particular. When a drug dependence arouses therapeutic concern, it is counted as a morbus. We are then dealing with a *morbid drug dependence*. This has two varieties. The first is a morbid psychological dependence. It occurs with such drugs as amphetamines, cannabis, and cocaine. It is characterised by a compulsive craving for the pleasurable experiences the drug arouses. The second variety adds to this psychological dependence a morbid physical dependence. Among the drugs responsible for it are heroin (and other opiates), alcohol, barbiturates, nicotine, and occasionally caffeine. Benzodiazepine dependence belongs to this variety.

A morbid physical drug dependence makes its appearance when a drug has produced a special kind of pathological change in the brain and the periphery, consisting of molecular transformations (mechanisms) which become so closely intertwined with the normal run of psychophysiological functions as to become indispensable. Unfortunately the molecular transformations are unstable, and have to be maintained by a regular supply of the responsible drug. Reducing the drug supply too abruptly plays havoc with the normal psychophysiological functions, and this leads to an avalanche of distressing and sometimes almost unbearable clinical symptoms. These are usually denoted by such terms as 'abstinence syndrome', 'withdrawal symptoms', or just 'withdrawal' (naming the cause but meaning the effect). Eventually, as we shall see, 'withdrawal symptoms' and 'withdrawal' are given a narrower designation to distinguish them, at least terminologically, from cognate symptoms occurring at the same time.

Let us consider heroin dependence as an illustration of a morbid physical drug dependence. An occasional heroin injection gives rise to transient molecular transformations in the brain. These do not constitute a disease because their clinical manifestations, consisting largely of a temporary analgesia and euphoria, do not arouse therapeutic concern. Indeed, they are therapeutically useful in alleviating intolerable pain. It is only when heroin injections are regularly repeated that the molecular transformations incorporate themselves as indispensable elements in normal physiological functioning. The transformations, or mechanisms, then constitute a disease, or disorder, namely a morbid physical drug dependence, which threatens the appearance of the clinical illness known as an abstinence syndrome.

Little or no attention is usually paid to the fact that physical drug dependence is not invariably of a morbid kind. There is also a therapeutic *physical drug dependence*. It receives little or no attention because it is not a morbus, nor a socio-medical nuisance. The patients concerned have no frantic compulsion to secure their therapeutic drug; they have, at most, an anxious need to "avoid the discomfort of [the drug's] absence" (World Health Organization, 1974) and to assure themselves that the drug is available to them.

Therapeutic physical drug dependence occurs when a drug is successful in the treatment of a chronic or intermittent morbus, with molecular anomalies causing functional clinical disturbances. This is best illustrated by a morbus which has been expressly called 'drug-dependent', namely the metabolic morbus of 'insulin-dependent diabetes'. The diabetic patients involved are obliged for therapeutic reasons to accept their dependence on regular insulin injections. It is through these injections that their diabetes becomes more or less clinically 'silent', or 'covert', or 'subclinical'. Stopping the insulin injections abruptly would not cause an abstinence syndrome. There would merely be a gradual return of the clinical manifestations of diabetes in their usual intensity and without any admixture of distressing new symptoms.

There are, of course, other functional disturbances which bring about a therapeutic drug dependence. Of particular interest in the present context is the morbus of epilepsy. Among the antiepileptic drugs which can keep this morbus in check is the benzodiazepine clorazepam. It is noteworthy that there has never been an outcry against the use of this benzodiazepine by epileptic patients who are therapeutically dependent on it. Epilepsy, after all, arouses a very much stronger therapeutic concern than drug dependence, even in the most determined abolitionists of drug enslavement.

Examples of other drugs giving rise to a therapeutic dependence in chronic or intermittent morbi are: vitamin B_{12} in pernicious anaemia, factor VIII in haemophilia, glyceryl trinitrate in angina pectoris, antacids in oesophageal reflux, β-adrenoceptor agonists in bronchial asthma, neuroleptic drugs in schizophrenia, and antidepressants and lithium in manic–depression.

The clinical condition for which benzodiazepines are most commonly prescribed consists of a mixture of anxiety symptoms, depressive worries, and sleep disturbances – a mixture that we shall term 'anxiety illness'. This illness does unfortunately not command much respect and therapeutic concern. It is, as we have seen, often viewed with disdain and disparagement as a mere weakness of character. The clinical manifestations of an anxiety illness betoken the existence of a disease in the form of pathological molecular changes in the brain. These may be no more than transient responses to disturbing experiences, in which case, psychological and perhaps also social help is indicated, but drug therapy may not be required. Indeed, if benzodiazepines or some other psychotropic drugs are prescribed, most patients do not persevere with them (e.g. Williams *et al*, 1982; Catalan *et al*, 1984; Williams, 1987).

Yet the pathological cerebromolecular transformations of an anxiety illness may establish themselves and acquire some autonomy, although still remaining, of course, under the influence of emotional experiences. When such pathological transformations persist and give rise to the constant or intermittent clinical symptoms of an anxiety illness, benzodiazepines may be administered successfully for a long period, leading to a therapeutic drug dependence.

Benzodiazepines can, however, also cause a morbid drug dependence, so that stopping their administration abruptly is followed by temporary and often very unpleasant abstinence symptoms. This was demonstrated by the application of large doses to animals. Such toxic amounts obviously caused pathological cerebromolecular changes which, like those after heroin injections, incorporated themselves as indispensable elements of normal brain functions. The pathological changes therefore had to be maintained at the risk of grave perturbations of cerebral activities. It then turned out that the non-toxic therapeutic doses of benzodiazepines which are given to human patients could have the same result. Patients with an anxiety illness would then have two kinds of pathological molecular changes in their brains: the original disorder responsible for the anxiety illness, and now a new disorder responsible for the morbid benzodiazepine dependence. The two disorders could then be expected to produce different clinical manifestations; one, the original anxiety illness, and the other, the new abstinence syndrome. The latter would run a time-limited course lasting, at most, until the drug and its metabolites had left the body and the drug-induced pathological changes had come to an end. This phase would then be followed by the return of the initial anxiety in its unmitigated form, as it was no longer muffled by benzodiazepines. It happens at times that an abstinence syndrome is not followed by anxious–depressive symptoms, perhaps because the initial diagnosis had been wrong or because the original molecular disorder had disappeared or become subclinical. In that case, the patients had, at least for some time, swallowed pills they did not, or did no longer, need, and had been unnecessarily subjected to an unpleasant abstinence syndrome.

The presence of two pathological mechanisms in the brains of patients with a morbid benzodiazepine dependence has usually been assumed in the literature (e.g. Owen & Tyrer, 1983; Rickels *et al*, 1983; Petursson & Lader, 1984). Yet there are difficulties with this assumption. In the first place, it predicts a difference between the clinical manifestations of an anxiety illness and those of an abstinence syndrome. Strenuous efforts have been made to establish this difference, but they have not been strikingly successful. Some apparently specific abstinence features have been pointed out as possibly distinctive, but it turned out that they did at times occur in healthy subjects, especially on stressful occasions, such as before an examination (Merz & Ballmer, 1983; Rodrigo & Williams, 1986).

Moreover, the clinical picture of the abstinence syndrome is also subject to psychological and social influences. There have, for instance, been 'pseudo-withdrawal' symptoms in patients who expected possible withdrawal symptoms and produced them, when this was not justified objectively (Winokur & Rickels, 1981; Tyrer *et al*, 1983). Moreover, a doctor's personal expectations can unwittingly have a suggestive effect on patients. This can happen to a keen crusader against the careless use of benzodiazepines. It may have happened to Ashton (1984), who found that the abstinence syndrome in her patients had unusually distressing components and could last "a year or more".

It is understandable that patients who still suffer from an anxiety illness after they had endured an unpleasant withdrawal procedure may look favourably on the assertion that their continuing symptoms had been drug-induced. This frees them from the stigma of having weak characters and being neurotic freaks. It allows them to feel that the blame does not lie with them, but with their doctors or the pharmaceutical industry who had failed to warn them of the vexatious morbid addiction which benzodiazepines may produce. Patients are now encouraged to take legal steps to obtain redress. One may therefore expect that compensation neurotic elements will further affect the clinical picture and muddy the waters. A sober assessment of patients who had been fully weaned from benzodiazepines has revealed that, one to five years later, 60% of them still had their anxiety illness and that about 50% had resumed some psychotropic medication (Golombok *et al*, 1987).

Another difficulty with the assumption that a morbid benzodiazepine dependence is based on the presence of two different pathological mechanisms in the brain results from this conjecture being too closely fashioned on the model of heroin dependence. When heroin dependence occurs in patients suffering from a painful disease, the drug does not directly affect the disease. It merely masks some of its clinical manifestations. It is possible to be otherwise with benzodiazepines. They may affect the anxiety-causing molecular disease directly, controlling it is a way that silences, or at least muffles, its clinical expressions. When this control is abruptly lifted, a molecular upheaval can then sometimes occur that manifests itself clinically in what has been called a 'rebound phenomenon'. It consists in a transient intensification of the anxiety illness. This rebound phenomenon was first described by Kales *et al* (1978), when benzodiazepine medication had been suddenly discontinued in patients treated for insomnia. It was soon noticed that patients with anxiety illnesses responded similarly (Kales *et al*, 1983; Fontaine *et al*, 1984; Lader & Lawson, 1987).

Rebound phenomena are not only observed with benzodiazepines. They have also been reported with tricyclic antidepressants (Kramer *et al*, 1961; Mirim *et al*, 1981; Charney *et al*, 1982); with lithium (Klein *et al*, 1981); with β-adrenoceptor blockers (Garbus *et al*, 1979; Rangno & Langlois, 1982); with antipsychotic drugs (Gardos *et al*, 1978); with L-dopa, corticosteroids, oral coagulants, and other drugs. All these medications are thus capable of producing a morbid dependence. Yet they have not been denounced on account of that, probably because they had never been overprescribed, perhaps because their rebound responses are not common and not usually severe, and perhaps because the medicinal need for them is widely appreciated, since they control illnesses which rouse much therapeutic concern.

Theoretically, there should be some difference between rebound phenomena and withdrawal symptoms. Rebound phenomena should consist of the intensified symptoms of the decontrolled disorder, whereas withdrawal symptoms should feature the opposite of the drug effects, including actual or possible side-effects. In the case of morbid benzodiazepine dependence, withdrawal symptoms (in a narrow sense) greatly resemble rebound phenomena, but also contain the additional feature of a perceptual hypersensitivity to light, sound, and touch, which is not a common ingredient of anxiety illnesses.

The great resemblance between rebound and withdrawal symptoms seems to speak in favour of the assumption that a morbid benzodiazepine dependence is due to just one kind of cerebromolecular disorder. Lader & File (1987) have advanced such a hypothesis. They state:

> "[We] argue that the two phenomena [of rebound and withdrawal] cannot be distinguished and therefore that each reflects the same common mechanism of dependence".

They mention that we already have a glimpse of some part of this mechanism as it contains a molecular formation that has been experimentally identified. It consists in:

> "high affinity, stereo-specific binding sites for the benzodiazepines. These sites are found on a supramolecular complex with γ-aminobutyric acid (GABA) receptors and with a chloride ionophore (channel across the cell membrane) which also has binding sites for drugs such as the barbiturates (Olsen, 1982)."

Lader and File go on to consider further particulars about the cerebromolecular pathology of the abstinence syndrome.

> "One possibility is that withdrawal [i.e. the cerebromolecular disease] is due to a change in endogenous ligands that act at the benzodiazepine receptor. The benzodiazepine receptor is unusual in that as well as the benzodiazepines that act there to lower anxiety levels and seizure thresholds, it can also mediate the action of the so-called 'inverse agonists' which have behavioural effects in the opposite direction, i.e. they increase anxiety and promote seizures. While no endogenous ligand has yet been identified with certainty, there is evidence that both a benzodiazepine-like and an inverse agonist-like ligand might exist." (See also File, 1988)

This account seems to provide an inkling of the cerebromolecular pathology that is involved in the pathogenesis of an anxiety-causing disease, in its control by benzodiazepines, and in its decontrol that issues in abstinence phenomena.

Not all patients who abruptly stop their benzodiazepine medication develop an abstinence syndrome – only some do. Research has shown that the incidence of abstinence syndromes, and therefore of morbid drug dependence, increases with the length of more or less continuous benzodiazepine medication. The actual figures published are unreliable, as they have been derived from variously biased, and often very small, samples of patients. According to Marks (1985*b*):

> "below 4 months [of regular benzodiazepine medication] the incidence of [morbid] dependence is virtually nil, unless alcohol, other sedatives, or narcotics are also being taken. Up to about one year's continuous use, the incidence of significant withdrawal phenomena is estimated to be less than 5%. Over one year of continuous use, the incidence appears to rise steeply."

Marks (1985*a*) says: "Even after many years of daily use a majority of patients experience either no problems or minimal problems". Trewin *et al* (1986), for instance, abruptly withdrew benzodiazepines "without any obvious clinical embarrassment" in 127 geriatric patients who had taken these drugs for years. According to Petursson & Lader (1984), the incidence of abstinence symptoms can be 25–45% after two years of regular benzodiazepine consumption, and 75% after six to eight years.

In general, it can be said that the likelihood of a therapeutic benzodiazepine dependence turning morbid increases with age, the severity of the anxiety-causing cerebromolecular disease, the number of social problems afflicting a patient, and the shorter the half-life of the benzodiazepine used. Other significant factors seem to be the length and regularity with which alcohol and psychotropic drugs, including benzodiazepines, had been used in the past. Rickels *et al* (1983) noticed that:

> "withdrawal incidence was considerably affected by the length of prior sedative-benzodiazepine therapy, ranging from 5% in patients with no prior drug therapy to 43% in patients with eight months or more of prior drug therapy."

Smith (1983) reported that 90% of patients with withdrawal symptoms had a past history of alcoholism, even when they were not currently drinking. It thus seems that prolonged use of psychotropic substances can affect the cerebromolecular system involved in the pathology of anxiety-causing diseases in such a way that some kind of precarious balance is established, which collapses with a flood of rebound symptoms when the psychotropic substance is suddenly and inconsiderately withdrawn. For this reason, it is a sound injunction to monitor psychotropic medication at regular intervals in order to keep the dosage and length of therapy as low and short as possible.

Early in the history of the present crusade against excessive benzodiazepine prescriptions, doctors were advised that withdrawal symptoms had nothing to do with a return of the, now uncontrolled, anxiety illness. (Rebound phenomena were still unknown then.) Therefore the patients should not be given further doses of benzodiazepines. They were therefore sternly left to suffer the misery of their abstinence syndrome, and doctors had an opportunity to study that syndrome closely. The result was an outpouring of papers describing morbid benzodiazepine dependence in detail. The medical world was impressed. Officialdom and the media took notice. The damnation of benzodiazepines was on its way.

Today it is recognised that abrupt drug withdrawal should be avoided, as far as possible. When abstinence symptoms occur, patients should be put back on benzodiazepines or some other suitable drug, preferably of a long-acting kind. Such medication should then be gradually and slowly tapered off in a samaritan rather than puritanical spirit. Whether this will be completely successful in the end depends on the chronicity of the anxiety illness involved. There is certainly a group of patients who need prolonged, and perhaps continuous, benzodiazepine medication, so that they can live a tolerable life and take fairly full advantage of their abilities. No dire harm is likely to befall such patients. As Tyrer & Murphy (1987) put it:

> "From present evidence, there is no unequivocal permanent handicap caused by benzodiazepines in short- or long-term dosage. . . . At the present state of knowledge it is too punitive to withdraw benzodiazepines from long-term users who do not want to stop treatment."

Unfortunately, the increasingly strident and threatening clamour against the therapeutic use of benzodiazepines compels doctors today to be unusually circumspect, and to temper their medicinal advice with a (recorded) caution of the side-effects patients might experience in the first few days (e.g. somnolence, clumsiness, perhaps an aggressive outburst), and of the possibility of a traumatic morbid dependence on prolonged medication. One cannot expect the general public to have much respect and therapeutic concern for patients with an anxiety illness. Yet they are in special need of our sympathy and understanding for the stigma they endure and the wretchedness they suffer, which can drive some of these unfortunates to seek a despairing exit through suicide.

Addendum

There is a belief abroad that benzodiazepines usually lose their therapeutic power during prolonged administration. There is no convincing evidence for this belief. Indeed, the evidence to the contrary is stronger. Whenever rebound phenomena occur, they prove that benzodiazepines had been active in suppressing the clinical expression of a cerebromolecular pathology. Moreover, when patients have been fairly well adjusted on benzodiazepines for a long time but succumb, after a successful withdrawal procedure, almost immediately to a modified recurrence of their anxiety illness, the proof that there had been a continuing therapeutic activity of benzodiazepines could hardly be stronger. Of course, it then also follows that the patients are in need of further medication and perhaps even of further prescriptions for benzodiazepines. This would help the patients, even though it is anathema to a narrow-minded damnation chorus.

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The Occurrence of Depression Following Mania

A Method of Predicting Vulnerable Cases

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In a retrospective analysis of 100 cases of mania (1981–1985), the incidence of subsequent depression was found to be 30%. Its occurrence was significantly associated with three factors: cyclothymic pre-morbid personality, family history of affective disorder, and past history of depression. By discriminant analysis, outcome could be predicted successfully in 81% of cases.

Kraepelin (1921) stated that depressive symptoms during the course of mania were unusual. More recently this has been challenged by Morgan (1972), who estimated that 60% of patients showed depressive symptoms during the course of their recovery from mania, with half of these being sufficiently severe to require treatment.

Clearly, it would be advantageous to be able to identify those particularly at risk: not only would this aid early detection, but it would also help rationalise management with antidepressant drugs where their use may be problematical owing to an inherent tendency to reintroduce mania, and where transient mood swings are common.

The present study aimed to discover the incidence of depression associated with recovery from mania, and to elucidate those factors that could discriminate between groups of patients likely to require and not require antidepressant treatment.

Method

A retrospective analysis of case-notes was made of all patients at High Royds Hospital with a discharge

TABLE I

A cross-tabulation of factors studied and their association with subsequent depression

	Total	*Non-depressed*	*Depressed*	*Significance*
Sex				
M	37	28	9	$\chi^2=0.52$, d.f. = 1, $P=0.47$
F	63	42	21	
First manic illness				
Y	18	11	7	$\chi^2=0.39$, d.f. = 1, $P=0.53$
N	82	59	23	
Past history of depression				
Y	72	45	27	$\chi^2=0.57$, d.f. = 1, $P=0.02$
N	28	25	3	
Cyclothymic personality				
Y	24	7	17	$\chi^2=22.58$, d.f. = 1, $P=0.0001$
N	76	63	13	
Family history affective disorder, first-degree relatives				
Y	22	14	8	$\chi^2=0.22$, d.f. = 1, $P=0.64$
N	78	56	22	
Family history affective disorder, all relatives				
Y	32	16	16	$\chi^2=7.62$, d.f. = 1, $P=0.005$
N	68	54	14	
Lithium therapy				
Y	65	46	19	$\chi^2=0.00$, d.f. = 1, $P=1.00$
N	35	24	11	
Phenothiazine only	47	30	17	See text
Butyrophenone only	33	21	12	
Combination	13	12	1	
Thioxanthenes only	6	6	0	
No neuroleptic	1	1	0	

diagnosis of mania during the period 1981–1985. If the patient had been admitted more than once, the most recent admission was taken as the index one. Subjects qualified for the study if they were between 18 and 69 years of age and satisfied Feighner's criteria for mania (Feighner *et al*, 1972).

Two groups of patients were identified by one investigator (J.C.R.): those who became depressed following an episode of mania (either immediately or in a period up to 28 days after euthymia, sufficient to require biological treatment and fulfilling Feighner's criteria for depression, apart from the requisite about duration of illness) and those whose recovery was not complicated by depression. The presence or absence of eight factors of possible predictive value was then determined by a second researcher (C.P.L.), who thereby remained relatively blind to the occurrence of depression.

Information extracted was as follows (criteria in parentheses):

(a) age (at time of index admission)
(b) sex
(c) past history of mania (previous hospital admission satisfying Feighner's criteria for mania (Feighner *et al*, 1972))
(d) past history of depression (previous hospital admission satisfying Feighner's criteria for depression (Feighner *et al*, 1972))
(e) presence of cyclothymic premorbid personality (physician's diagnosis or data in case-notes fulfilling DSM–III criteria (American Psychiatric Association, 1980))
(f) family history of affective disorder (bipolar or unipolar resulting in hospital admission)
  (i) first-degree relatives
  (ii) any relative (first or second degree)
(g) lithium carbonate treatment (while in the manic phase and having therapeutic plasma levels)
(h) neuroleptic used (multiple or sequential therapy allowed for)
  (i) phenothiazine
  (ii) butyrophenone
  (iii) thioxanthene.

Cases were excluded if they had not been followed up for at least one month following euthymia or if there was insufficient information in the notes to be able to complete all parts of the research check list.

Results

One hundred and thirty-six patients with the appropriate discharge diagnosis were found. Eleven sets of case-notes could not be traced, and 25 patients were excluded for not fulfilling criteria or for having incomplete information in the case records.

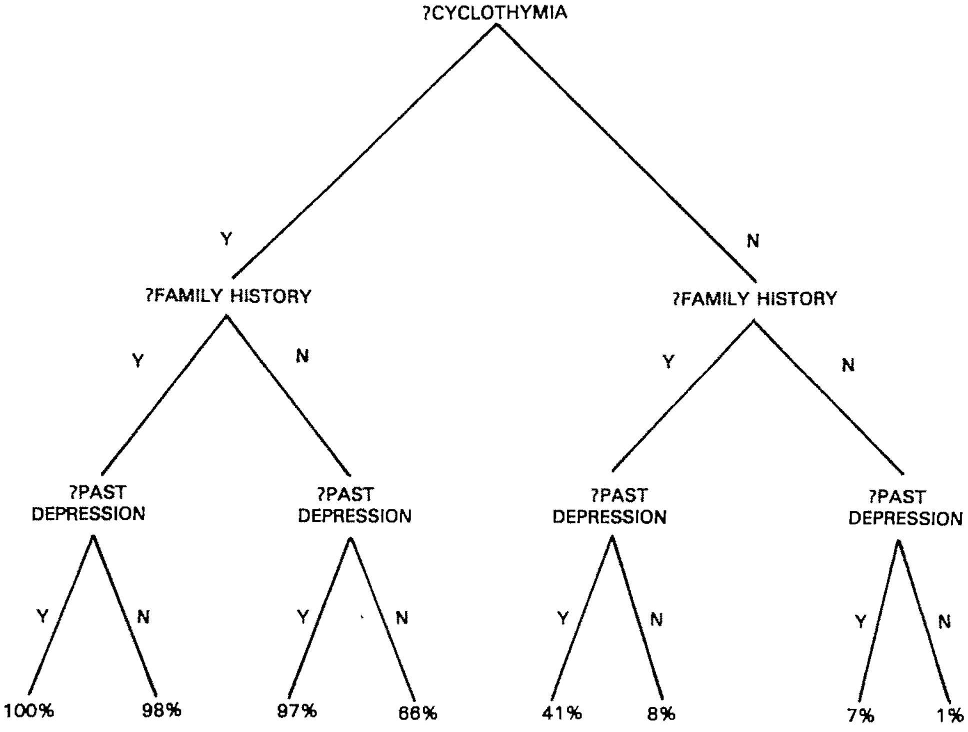

FIG. 1 An algorithm for prediction of the relative probability of depression

One hundred cases entered the study: 63 females, mean age 47.95 years (s.d. 13.11), and 37 males, mean age 36.24 years (s.d. 12.39). There was no significant difference in the median age of the depressed (30%) and non-depressed (70%) groups (Mann–Whitney U-test, 2-tailed, $P=0.64$). A cross-tabulation of putative predicting factors and occurrence of depression can be seen in Table I.

There was no effect on the likelihood of depression among patients given either a phenothiazine or a butyrophenone as sole therapy ($\chi^2=0.048$, d.f.1, $P=0.82$). Patients receiving a combination of neuroleptics were less likely to become depressed than those receiving monotherapy ($\chi^2=5.9$, d.f. $=2$, $P=0.052$). In the small number receiving a thioxanthene as sole therapy, there was a non-significant decrease in subsequent depression compared with patients receiving one of the other drugs (Fisher's exact test, $P=0.08$).

The contingency tables for past history of depression, cyclothymic personality, and family history of affective disorder in first- and second-degree relatives were found to have highly significant differences in the proportions of depressed and non-depressed patients in the two categories in each table.

A multivariate analysis was carried out by Fisher's (1936) classic method of linear discriminant analysis, with Wilks' method (Tatsuoka, 1971) for the stepwise selection of variables, and using the implementation by the SPSS statistical package (Norusis, 1986). This analysis showed that cyclothymic personality was the most important predictor of the subsequent development of depression (50% weighting in the canonical discriminant function). Family history of affective disorder (26% weighting) and past history of depression (24% weighting), together with cyclothymia, could successfully categorise 81% of patients. The algorithm in Fig. 1 shows the relative probability of depression with various combinations of these factors. The actual rate of misclassification of 19%, when compared with the expected misclassification rate of 41% (1 minus prior probability of classification based on the size of a given group), suggests that the discriminant function was more effective than chance in predicting the outcome.

Discussion

Short-term prognosis in manic–depressive illness has hitherto shown little connection with a wide variety of demographic, clinical or genetic factors (Taylor & Abrams, 1981). Our study looked at one aspect of prognosis, namely the occurrence of depression in the first month following mania. Its incidence was shown to be 30%, and short-term outcome could be successfully predicted in 81% of cases.

Pre-morbid personality has previously been associated with prognosis in manic–depressive illness (Rennie, 1941). This is the first study, however, to identify that a cyclothymic premorbid personality is a major risk factor for the development of depression subsequent to mania. This finding may indicate a true vulnerability, may represent unnecessary treatment of 'normal' mood swings, or may be the result of inadequate treatment.

Two further factors could aid the prediction of those patients who would be likely to become depressed soon after a manic illness. These were family history of affective disorder and a past history of depressive illness.

The genetic basis in manic–depressive illness is well established. Mendelwicz *et al* (1972) showed that a more severe form of illness was seen in those patients with a positive family history. Our study supports this, and in addition shows a highly significant association between family history and post-manic depression.

That a past history of depression renders one more likely to be depressed following mania is not unexpected. Bias might be encountered in this association due to subtle alterations in treatment thresholds, and this cannot be ruled out. Whether this was a first manic illness or a recurrent disorder was found to be unimportant, as were the age and sex of the patient.

Neuroleptics have been implicated in the pathogenesis of depression, with butyrophenones singled out as the most likely culprit (Morgan, 1972). No evidence is seen in this study to support that assertion, as the proportions of depressed and non-depressed patients among those treated with a butyrophenone and among those treated with a phenothiazine were similar.

It appears, however, that a subsample of patients receiving both drugs showed less post-manic depression. This association is likely to be spurious, and probably will reflect characteristics of the illness in this group rather than any drug effect. Patients receiving more than one drug during a manic episode will be different in many ways. They may have multiple therapy as a result of greater initial behavioural disturbance or a more resistant manic picture, or for other more subtle reasons. No episodes of depression were seen in the group receiving thioxanthenes: in view of the small numbers involved, this does not reach statistical significance.

Lithium is an effective prophylactic agent in both bipolar and unipolar disorder and there is some evidence that it possesses an acute antidepressant effect (Schou, 1986). One would expect therefore that it would reduce the frequency of depressive episodes following mania. No such effect was seen in our study.

The findings here have an important clinical message, in that any patient who has a premorbid history of cyclothymia together with either a positive family history or previous depression is at a high risk of developing depression ($P=0.97$) and should be monitored closely. It remains to be seen, though, whether or not patients without any of these risk factors have depressive symptoms that are merely transient and do not require treatment.

We feel these results are interesting and provide the stimulus for further research. In particular, the application of discriminant analysis and risk prediction is one which has considerable potential for clinical usefulness. The areas of possible bias already discussed and the errors inherent in any retrospective analysis may prove the associations to be unreliable. We plan, therefore, to undertake a prospective study to validate these findings, using more rigorous operational methods and criteria.

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Alexithymia, Masked Depression and Loss in a Holocaust Survivor

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A woman who suffered multiple losses in childhood and adolescence became depressed 40 years later, after a series of new losses. Concomitant alexithymic features caused a masking of her depression by somatic symptoms. The relationships between alexithymia, masked depression and loss are discussed.

Alexithymia is a condition of constricted ability to recognise and express feelings or emotional states. Also, alexithymic people have a paucity of fantasies, few dreams, and a tendency to think in an operative, non-symbolic manner. They have little contact with their own psychic reality and cannot discriminate between emotional states and bodily sensations. Instead, they communicate psychological distress by means of somatic complaints (Sifneos, 1972; Lesser, 1981). The aetiology of alexithymia is not clear; theories consider such mechanisms as hereditary and constitutional factors, neuropsychological and neuroanatomical defects, and psychodynamic and sociocultural influences (Nemiah, 1977; Taylor, 1984). Alexithymia is not necessarily a stable personality trait and can be a temporary and transient feature in face of stress and threat (secondary alexithymia) (Freyberger, 1977; Krystal, 1979).

Masked depression is a depressive state in which the classic, affective and cognitive symptoms are hidden behind various somatic, behavioural or hypochondriacal manifestations (Lesse, 1968; Lopez-Ibor, 1972). The reasons for the masking of depressive symptoms may be psychodynamic, familial, sociocultural or neuropsychological (Katon *et al*, 1982; Lesse, 1983).

Patients with masked depression and people with alexithymia share the inability to express their emotions in words. In both conditions somatisation is used to express feelings and to communicate distress. The following case report demonstrates the inter-relations between two common clinical conditions.

Case report

A 58-year-old woman was referred for psychiatric evaluation after a thorough gastroenterological and medical investigation failed to disclose the reasons for her three-year lack of appetite, weight loss, nausea and abdominal discomfort. The gastroenterologist was also impressed by the resistance of the condition to various treatments. The patient was a married mother of three adult children. She grew up in Europe as the youngest of three siblings. At the age of 12 years she unexpectedly lost her mother, who died instantly of a sudden heart attack in her presence. Soon after her mother's death, World War II broke out and the patient went through the horrors of the Holocaust. She had to hide during the war, being in constant danger of disclosure and deportation to a concentration camp. In 1941 she narrowly escaped this fate, but her sister, to whom she was very close, was caught and sent to a camp, where she subsequently died. Later she worked as a member of a rescue team, and was involved in evacuating bombardment casualties. As the war went on she was witness to the deportation and death of almost all her relatives and acquaintances. After the war she emigrated to Israel. She said: "I could function normally because I built a partition between my mother's death and myself. Later I succeeded in repressing the Holocaust completely. I did not even dream about it. I always performed my tasks perfectly. This was my salvation."

Her symptoms began at the age of 55, soon after she and her husband moved to Jerusalem from another town, in order to be near their daughter, who had just given birth to a severely handicapped and retarded child. The patient had to quit her job as a principal school secretary, a job that was highly valued by her because it gave her much satisfaction and recognition. She also lost contact with many acquaintances and friends.

Soon after her move, her grandchild died and her daughter and son-in-law left the country for an overseas job. The patient became increasingly dissatisfied with her life and excessively preoccupied with her health. She had numerous medical examinations because of bowel trouble, weight loss, chest pain and nausea. She could not sleep properly and was restless. Although the patient denied any feelings of depression or psychological distress, the family insisted that she saw a psychiatrist. The psychiatrist prescribed a minor tranquilliser and referred her to a psychotherapist. The patient had been in therapy for over one year without any change in her condition, and one additional year had lapsed before the present referral.

During the interview, the patient denied feelings of sadness or depression but complained about her bodily symptoms. In addition, she blamed herself for being ill, for not being able to function as well as she should and for being a burden to her family. She did not agree to have any "talking cure" but consented to pharmacotherapy. At that time her Hamilton Rating Scale for Depression score was 23 (moderate depression) (Hamilton, 1960) and her BIQ alexithymia score was 5/8 (Sifneos, 1973). The main alexithymic feature was a complete lack of emotional expression, both verbal and non-verbal. She claimed to have no dreams, and had a markedly restricted ability to talk about fantasies and other themes which were not strictly concrete. She denied any possible causative connection between guilt, grief, shame and physical sensations. Her world was strictly cognitive and somatic, with no place for emotions.

A masked depression was suspected and the patient was treated with imipramine (Tofranil) (150 mg daily). After two months of treatment the patient recovered completely. She was free of all somatic symptoms and was so happy and cheerful that the possibility of a hypomanic reaction was considered. Her Hamilton score was 1. She continued with the drug for a further six months. After cessation of the drug the remission continued. At follow-up one year after the initial examination, she was in perfect physical and mental health. Her BIQ alexithymia score was 2/8, consisting of a paucity of dreams and a somewhat limited ability to fantasise, but there was no longer a lack of emotional expression. About her illness she said: "I think that I did not really feel depressed, or maybe I did not want to admit to myself that I was depressed. I told the doctors that I was not depressed although I knew that I was not well, but I did not know that it was a depression. I feared that I was becoming crazy. I always thought that if I could stay sane after all that I probably must be insane."

By chance, the last follow-up meeting with the patient fell on the national Holocaust memorial day. The patient wept when she talked about her feelings. It was obvious that she was not alexithymic any more – she could not have expressed her feelings better than she did that day.

Discussion

This case report illustrates the reversibility of the alexithymic pattern in a patient with masked, somatised depression. While depressed, the patient could not express her feelings verbally and, instead, she somatised and complained of physical distress. She talked about the circumstances of events, but not about their emotional meaning to her. In addition, she showed very limited ability to use fantasy. After only a few months, without any specific psychotherapy, this pattern changed completely as her depressive state lifted.

This patient suffered multiple severe losses in her early years. The loss of the mother before age 15 is believed to be a major predisposing factor for depression in women, and childhood object loss might also predict adult character pathology (Brown & Harris, 1978).

The experience of the Holocaust terrors during the war must be regarded as massive, catastrophic psychic trauma. Between the ages of 12 and 18, the patient lost her mother, sister, home, country, identity and property. Survivors of massive psychic trauma can suffer character damage, including a tendency to alexithymia (Krystal, 1979).

According to her own statement, our patient could remain sane and function normally only because she built defences against recognition and expression of feelings: she was mildly alexithymic. These defences functioned well until she again suffered a series of losses more than 40 years after the first series of disasters. Then, under the new pressures, these defences became more pronounced and the alexithymic pattern was now so strong that the patient could not perceive or express the cognitive or affective components of her major depression. She presented with masked depression. After antidepressants relieved her depression, the alexithymic pattern resolved partially.

Alexithymia is not necessarily a rigid and stable personality trait: it can wax and wane. Neither is it an obligatory or universally present pattern in masked depression, but, understandably, people who have an alexithymic pattern will conceal emotions also, or especially, when they suffer from depression. Therefore, it is probable that alexithymic people are more prone than others to suffer from masked depression.

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Two Cases of Agranulocytosis on Addition of a Butyrophenone to a Long-Standing Course of Phenothiazine Treatment

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Two cases of agranulocytosis occurring after addition of a butyrophenone to a course of phenothiazine treatment are reported and possible mechanisms for this interaction are discussed.

Agranulocytosis is a well-documented adverse effect of phenothiazine administration (Vincent, 1986). Important factors are the total amount of drug given and the duration of administration. Agranulocytosis usually occurs within the first three months of therapy (Pisciotta, 1971; Marcus & Mulvihill, 1978) and the relationship with the cumulative dose has been emphasised (Ananth *et al*, 1973). Agranulocytosis following prolonged administration has been rarely reported (Denber, 1970, Pisciotta, 1978). We report two cases where agranulocytosis developed in patients with a long previous exposure to phenothiazines, treated for the first time with a combination of phenothiazines and a butyrophenone.

Case reports

Case A

A 50-year-old man with a history of recurrent episodes of depression and paranoid psychosis was admitted to psychiatric hospital during a relapse. He had previously been treated with chlorpromazine, clomipramine and electroconvulsive therapy. Flupenthixol decanoate had been administered long-term on an out-patient basis, and he had received a total of 67 g chlorpromazine over the two years before admission. Treatment initially was chlorpromazine (150 mg t.d.s.). After one week the dose was increased to 150 mg q.i.d., and after a further ten days increased to 300 mg q.i.d. for a further week. Droperidol was given over the last four days in dosages of 10–20 mg to a total of 90 mg.

The patient was then noted to be unwell. On examination he was icteric, with oral candidiasis. His pulse was 110 per min and regular; temperature was 40 °C. Widespread crepitations and expiratory rhonchi were present. A neutropenia with less than 1% neutrophils in a total white blood count of 1×10^9 per litre was found. Haemoglobin and platelets were normal. A throat swab yielded *Staph aureus*. All cultures from blood, urine and sputum were negative. Reduced cellularity with myeloid maturation arrest consistent with drug-induced agranulocytosis was seen in bone marrow. Nursing was in a laminar flow isolation unit. Treatment was with intravenous netilmicin and flucloxacillin and with chest physiotherapy and nebulised inhalers. His condition improved rapidly, becoming apyrexial three days after his admission to the unit. Daily blood counts revealed a persistent rise in neutrophils, and eleven days after becoming ill he had a normal blood film and a white blood count of 7×10^9 per litre with 60% neutrophils. During this period his psychiatric symptoms remitted and he was discharged on no psychotropic medication.

Case B

A 60-year-old woman with a history of recurrent schizoaffective psychosis was admitted during a relapse. She had previously been treated with depot phenothiazines, lithium carbonate and chlorpromazine, the treatment with chlorpromazine being extensive and including a total of 11 g over the three months before admission. She was treated with chlorpromazine (200 mg t.d.s.) and droperidol (20 mg) if required. A total of 100 mg of droperidol was given. Her regular fortnightly injection of 50 mg fluphenazine decanoate was continued. After ten days she became suddenly unwell and complained of acute dyspnoea. On examination she had a temperature of 39 °C and a tachycardia of 140 per min; bilateral rhonchi in both lung fields with coarse crepitations at the left base were heard on auscultation. The chest X-ray showed patchy opacities at the left base. No neutrophils were detected in a white blood count of 0.7×10^9 per litre. Haemoglobin and platelets were normal. Hypercellular marrow with a marked increase in megakaryocytes was found on bone-marrow aspiration. Myeloid activity was profoundly depressed. Blood cultures were all negative. *Staph aureus* was cultivated from swabs from skin pustules. All other cultures were negative. Intravenous Augmentin, gentamicin and metronidazole were started and she was barrier-nursed.

Intravenous benzyl-penicillin was added the next day. Her condition steadily improved. She became apyrexial after five days and her white blood count was 1.8×10^9 per litre with 60% neutrophils after ten days. During this episode her psychotic symptoms remitted and she was discharged on no psychotropic medication.

Discussion

Agranulocytosis can occur in patients with long-term exposure to phenothiazines, with a significant mortality (Pisciotta, 1978; Davis, 1985), but it remains unclear why this should occur in patients who have previously tolerated phenothiazine treatment over long periods. One possible explanation is that the bone marrow in these individuals compensated for the effect of chlorpromazine in relatively low dosage and that decompensation occurred because of an increase in total dosage. It is also possible that droperidol inhibited metabolism of chlorpromazine and thus caused an increase in dose. We are unaware of any previous reports which substantiate this. The Committee for Safety of Medicines has no reports of droperidol causing agranulocytosis to date, although this has been reported with haloperidol. Droperidol is now the drug of choice in psychiatric emergencies (Ayd, 1980) and is therefore increasingly commonly used in combination with other psychotropic medication.

Despite its comparative rarity, agranulocytosis should be suspected in all patients receiving phenothiazines, regardless of previous treatment, if they become physically unwell. Long-term monitoring of blood counts with phenothiazine use is not recommended, whereas routine blood counts on admission or when physical illness is suspected can provide a valuable baseline. Combinations of different classes of antipsychotic drugs are very rarely, if ever, justified (Davis, 1985). Combinations cause difficulty in determining exactly which drug provoked the reaction. All drugs given at the time of the reaction tend to be avoided in future, possibly unnecessarily. In the two cases reported, agranulocytosis developed after a butyrophenone was added to treatment with phenothiazines. It remains to be seen whether this association will prove to be spurious or causal.

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Cholinergic Syndrome following Anticholinergic Withdrawal in a Schizophrenic Patient Abusing Marijuana

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A 27-year-old neuroleptic-stabilised schizophrenic patient presented with a three-day history of psychomotor retardation, disturbed sleep, and social and emotional withdrawal following reduction of his anticholinergic dosage; his symptoms had intensified after an increase in neuroleptic dosage, based on a diagnosis of psychotic decompensation. Recognition of a cholinergic syndrome and institution of appropriate anticholinergic treatment resulted in rapid improvement. The clinical distinction between a cholinergic overdrive state and schizophrenic exacerbation, while sometimes difficult, can be critical in selecting appropriate management.

The recognition of withdrawal reactions following discontinuation of psychotropic medications with anticholinergic properties is important in the treatment of various psychiatric disorders. Rapid withdrawal especially may result in a clinical syndrome characterised by bradykinesia, motor retardation, slowed thinking and speech production, lassitude, sleep disruptions, nightmares, emotional withdrawal, irritability, dysphoria, nausea, vomiting and diarrhoea (Dilsaver *et al*, 1984*a*). The mechanism is believed to be central and peripheral, cholinergic hyperfunction secondary to regulatory changes in muscarinic receptors occurring as a result of sustained anticholinergic blockade (Dilsaver *et al*, 1984*a*; Gardos *et al*, 1978). Patients who use marijuana may be at a higher risk for development of this syndrome (El-Yousef *et al*, 1973).

The anticholinergic withdrawal syndrome resembles the negative schizophrenic syndrome in many important respects (Crow, 1980*a*,*b*; Andreasen, 1982; Greden *et al*, 1987). Its occurrence in a schizophrenic patient may be mistaken for psychotic decompensation and result in inappropriate treatment. We report the syndrome in a marijuana-abusing schizophrenic patient.

Case report

Mr A, a 27-year-old male janitor with a two-year history of paranoid schizophrenia and a several-year history of cannabis abuse, was brought to the University of Michigan Medical Center psychiatric emergency room by his wife, because of a three-day history of increasing confusion, sluggishness, inability to work, feeling "frozen", irritability, disturbed sleep with nightmares, social and emotional withdrawal, and inability to perform the activities of daily living without assistance. There was no current evidence of delusions or hallucinations, suspiciousness, or ideas of reference. The patient had been in stable remission, with good occupational and fair social functioning on treatment with thiothixene (30 mg per day), imipramine (150 mg per day), and benztropine (4 mg per day). Two days before the appearance of the above symptoms, however, his out-patient psychiatrist had reduced the dose of benztropine to 1 mg per day because of concerns about overuse. The emergency-room psychiatrist diagnosed a psychotic exacerbation, abruptly discontinued the imipramine, and replaced the thiothixene with 30 mg of haloperidol per day, thereby doubling the effective neuroleptic dosage. The patient's symptoms progressively worsened, and he was admitted to the University of Michigan Schizophrenia Program two days later. The patient had last smoked marijuana one week before admission.

On examination, he was reasonably well groomed, sat slumped in his chair and displayed severe retardation of bodily movement and speech, gave mere yes or no answers to all questions after a prolonged latency, and reported a marked slowing of thought processes. His face was immobile and his affect was flat; despite his psychomotor deceleration, he was irritable and jittery. He had no involuntary movements, restlessness or rigidity, and he denied experiencing delusions, hallucinations, ideas of reference, thought control or other Schneiderian first-rank symptoms. He also reported the absence of depression or suicidal ideation. Formal testing of his cognitive functions was difficult, but he appeared orientated with respect to time and place. His vital functions were stable and no physical abnormalities were detected.

After reviewing all information, we formulated a tentative differential diagnosis of cholinergic syndrome versus akinesia. We discontinued haloperidol and restarted treatment with thiothixene at the previous dosage of 30 mg per day. The dosage of benztropine was increased to 2 mg p.o. t.d.s. and 2 mg orally as needed, not to exceed 10 mg per day. His symptoms remitted rapidly. Within the next few days, the patient became relaxed and verbal, his affect brightened and he became more expressive, irritability decreased and his speech and thought returned to normal. One week after admission, he had returned to baseline according to him and his wife. Despite the fairly high dosage of benztropine, he remained afebrile, his pupils were equal and reactive, and his pulse did not increase by more than 10 beats per min and was always regular. At no time did he report any psychotic or depressive symptoms. He was observed for another week and discharged on treatment with thiothixene 30 mg per day, and benztropine 2 mg p.o. t.d.s. He has returned to work, is asymptomatic and is functioning normally on this regime one month later.

Discussion

Several factors may have contributed to a state of cholinergic overdrive in this patient. The dosage of benztropine, an anticholinergic agent, was abruptly decreased in a patient who may have already been susceptible to the development of a cholinergic syndrome because of chronic marijuana abuse (Dilsaver *et al*, 1984*b*). We believe that symptoms of a cholinergic syndrome resulted and these intensified even more following abrupt discontinuation of imipramine (with moderate anticholinergic activity), and substitution of haloperidol for thiothixene. The symptoms resolved rapidly with anticholinergic 'replacement' treatment. While some authors may suggest that a diagnosis of akinesia may have been in order (Rifkin *et al*, 1975), akinesia is an extrapyramidal syndrome that can result from dopaminergic underactivity or cholinergic overactivity. Akinesia is a behavioural diagnosis and cholinergic overdrive the probable underlying pathogenetic mechanism in this case, and the two terms may thus reflect different aspects of the same phenomenon (Tandon & Greden, 1987; Tandon *et al*, 1988).

The case highlights the importance of careful differentiation between a cholinergic overdrive state and exacerbation of the schizophrenic illness. This differentiation is especially difficult when patients present with predominantly negative symptoms, as was observed in this case. Distinguishing between a cholinergic syndrome produced by drug withdrawal and psychotic decompensation is sometimes difficult, but can be critical in selecting appropriate management. A careful history, specifically noting recent medication changes, can often point to the correct diagnosis. Clinicians should be sensitive to the possibility of development of cholinergic overdrive in a schizophrenic patient due to a variety of mechanisms. Although it is sometimes difficult to distinguish from schizophrenic exacerbation, the cholinergic syndrome responds rapidly to aggressive anticholinergic treatment when accurately diagnosed. The case also points out one of the risks of cannabis consumption in schizophrenic patients (Treffert, 1978).

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De Clérambault's Syndrome (Erotomania) in Organic Delusional Syndrome

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A patient with de Clérambault's syndrome (erotomania) following brain damage and epilepsy is described. The delusion appeared after brain surgery for subarachnoid haemorrhage, and remained chronic. Erotomania in this patient may be judged to be aetiologically related to organic brain damage.

De Clérambault, in the 1920s, described the most well-known of the 'erotic delusions' as "pure erotomania". This syndrome is characterised by the 'fundamental postulate' of a woman having the conviction of being in amorous communication with a person of higher rank, whom she claims was the first to fall in love (Enoch & Trethowan, 1979). The delusion becomes chronic, and secondary or mixed forms can occur.

Erotomania has so far defied precise psychiatric classification. Although de Clérambault delineated a pure form of the syndrome, most modern writers tend to consider it as related to one of the major psychoses, i.e. schizophrenia or the affective disorders. The nosological controversy may in part be due to the poor description of pre-morbid history, personality and phenomenology. The revised DSM–III (DSM–III-R; American Psychiatric Association, 1988) classifies it as a specific type of delusional disorder.

Until recently, few cases of erotomania have been reported where there was an association with organic pathology. I present a case of erotomania in a patient with organic delusional syndrome.

Case report

Miss K., a 29-year-old right-handed single female, was found on referral to have erotic and paranoid delusions. She believed that she was deeply in love with a man who worked as an estate agent, from whom she rented a flat. She also believed that he was deeply in love with her and wanted to marry her, but was prevented from doing so because of pressure from "the DHSS and others". She pestered him with letters and telephone calls to such an extent that he had to move to another city, but she managed to find him. The man strongly denied any involvement with her, apart from the time he rented her the flat. She also believed that people were spying on her and trying to kill her.

In one incident, she wrongly accused a man of trying to rape her.

The patient had been diagnosed as having epilepsy following brain haemorrhage, when she was 25 years old. At that time, she developed headaches, nausea and vomiting while having sexual intercourse with her boyfriend. Subsequently, a large haematoma in the right temporal lobe with a superficial right parietal arteriovenous malformation was diagnosed. The haematoma was evacuated and the arteriovenous malformation branching from the right middle cerebral artery was excised. She made a good recovery, but was left with a left-sided hemiparesis and a left homonymous hemianopia, sparing the macular. She developed the epilepsy three months after the operation, and this was treated first with phenytoin and later with carbamazepine (600 mg daily).

A few months after the operation, her behaviour started to change gradually. It was described as "bizarre" for most of the time, and she was said to be "not her normal self". At age 27, she became resentful and aggressive towards her mother. She became a nuisance to neighbours, collapsing on their doorsteps, and she presented herself quite frequently to several accident and emergency departments, claiming that she had had another brain haemorrhage.

On referral, she was found to have a rather peculiar facial appearance. She has a brachiocephalic skull and hyperextensible elbows and knees, but her symptoms do not resemble any recognisable syndrome. An EEG showed a right temporal epileptic focus, but a CT scan was normal. Psychometric tests showed evidence of parietal lobe damage and cognitive impairment. Her WAIS scores were: verbal 98; performance 67; full scale 84. Her pre-morbid IQ was above average. In the Benton test, she showed cognitive impairment. On the Wechsler Memory Scale, her short-term memory was intact for simple material, but impaired for complex material.

Before her brain haemorrhage, she had no history of psychiatric illness. Her pre-morbid personality was outgoing and extrovert. She had drunk heavily since her teens and had had a one-off experience with a hallucinatory drug. She had had many heterosexual relationships, and was described as sexually promiscuous. She often acted in an impulsive way. She had had a termination of pregnancy four months before her brain haemorrhage. She had also experienced two losses in her life: her father, to whom she was very close, died when she was 20 years old; and her boyfriend left her after a seven-year relationship, following her brain haemorrhage.

She was treated with flupenthixol decanoate, which helped her paranoid delusions, but her erotomania remained unchanged. In addition to flupenthixol, her maintenance medication included carbamazepine for her epilepsy. Other management interventions included attendance at the day hospital and several attempts at retraining for a suitable job.

Discussion

This patient met the DSM-III-R criteria for organic delusional syndrome and erotomania. Her epilepsy started three months after her brain damage; several months later she developed more general delusional symptoms, and erotomania was diagnosed about three and a half years later. The average latent interval between the development of epilepsy and the emergence of the symptoms is usually 14 years (Slater *et al*, 1963). Most authors consider that the shorter the interval between head injury and the development of psychosis, the stronger is the likelihood of the conditions being linked (Weller, 1985).

Few cases of erotomania with organic aetiologies have been reported. Recently, Signer & Cummings (1987) reported two cases of erotomania in organic affective disorder. They also stated that epilepsy with partial complex seizures and temporal lobe foci appears to be particularly common among patients with focal lesions and erotomania. Among patients with organic delusional disorders, most of those with Capgras symptoms have had lesions involving the right hemisphere, whereas a majority of patients with Schneiderian first-rank symptoms have had lesions involving the left hemisphere (Cummings, 1985). The patient described here represents the only reported case of erotomania with clearly demonstrable temporal and parietal lobe damage in the right hemisphere and associated epilepsy. Of the six cases reported by Schachter (1977), one had head trauma (with fracture of the right temporal bone), and one exhibited symptoms consistent with epilepsy. A third case had left temporal lobe epilepsy and a fourth had a deep epileptogenic focus due to sphenoid wing meningioma (laterality unspecified).

De Clérambault's syndrome has been reported in patients with alcoholism (Feder, 1973; Schachter, 1977). This patient continues to abuse alcohol to a marked degree, as she has done in the past. She also had an abortion four months before her brain haemorrhage. Erotomania following abortion (Balduzzi, 1956) and ingestion of oral contraceptive (Lovett Doust & Christie, 1978) have also been reported, but the gap between the abortion and the erotomania was about four years in our patient.

Ellis & Mellsop (1985) concluded that most cases of erotomania occur in the setting of schizophrenia, but Signer & Swinson (1987) considered that the literature supports a predominant role for severe affective disorder. In our own analysis, out of a total of 80 diagnoses given to 62 patients with erotomania, 35% were for schizophrenia, paranoia and paraphrenia, 22.5% for affective disorder, 21.3% for organic disorders and 10% for neurotic disorders. These figures add support to Ellis & Mellsop's (1985) observations that de Clérambault's syndrome is an aetiologically heterogeneous disorder and, like Schneiderian first-rank symptoms, may be seen in a variety of psychotic conditions.

More cases with full details need to be reported for the nature and the aetiology of erotomania to be understood.

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Delusions of Pregnancy in Men

Case Report and Review of the Literature

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The case of a young, unmarried boy, who had moderate mental retardation, epilepsy, and post-ictal psychosis, is described here. During the psychosis, he believed he was pregnant, and had related behavioural disturbances. The review of other such cases reveals that organic brain damage was evident in all cases. Brain damage seems to be the more likely causative factor than psychodynamic factors.

The first case involving a delusion of pregnancy was reported by Esquirol in the 19th century (Vie & Bobe, 1932). Delusions of pregnancy in men are relatively rare, and have been occasionally reported as symptoms of a wide variety of psychotic states, including schizophrenia, melancholia, senile dementia, and general paresis, and following encephalitis (Baonville *et al*, 1935; Focquet, 1935; Jacobson, 1950; Neveu & Boyer, 1950; Alliez *et al*, 1956; Jenkins *et al*, 1962). The small number of recorded instances seems to be very small, and although there may be some common psychodynamic link determining the content of the delusion, this state does not appear to bear any real relationship to the Couvade syndrome, in which almost by definition the sufferer does not entertain the idea that he is pregnant (Enoch *et al*, 1967).

Delusions of pregnancy have been reported both in single and in married men, without, in the latter, bearing any definite relationship to their wives' pregnancies. Baonville *et al* (1935) described two cases: one was a 73-year-old man suffering from chronic organic brain syndrome; the other was a 44 year-old depressed patient. Marchand (Alliez *et al*,

1956) noted that men with general paresis frequently had the idea that they were pregnant. Alliez *et al* (1956) described another patient who thought he had multiple pregnancy and would report that the children were moving in his abdomen. Neveu & Boyer (1950) described a patient with post-encephalitic Parkinsonian syndrome who expressed delusion of pregnancy. The latest case of delusion of pregnancy was reported 25 years ago by Jenkins *et al* (1962). They reported a 19-year-old single boy who was "very confused, disoriented, incoherent and irrelevant" and had low IQ (verbal intelligence recorded as 61 on Wechsler's Adult Intelligence Scale).

It is difficult to comment as to whether delusions of pregnancy in unmarried (or married) men have been subsequently encountered clinically or not, but somehow for the last 25 years no cases have been reported. The presentation of delusion of pregnancy in a young unmarried Indian male is reported here. Also, the possible aetiological mechanisms for the development of such a phenomenon, which are evident from the present case and the previously reported ones, are discussed.

Case report

Mr A., aged 23 years, an unmarried man educated up to third class (three years of schooling), was brought by his father and uncle to our out-patient clinic at Bangalore. The father and uncle reported that Mr A. had been highly disturbed for seven days. The onset was sudden and there were no psychological precipitating factors. The patient had become excited and overtalkative (mainly irrelevant) and was shouting. He reported a sensation that someone was pressing his chest and that he had a child in his abdomen. He was very disturbed, as he heard many voices calling him but could not see anybody around. He repeatedly mentioned that someone had given a child to him and that he had "conceived". He cried incessantly and requested his parents to forgive him as he had committed this immoral act (of bearing the child). He denied any sexual assault. He did not stop his shouting despite frantic reassurances about this impossible happening by his parents and relatives. He did not sleep for three days and ate very little. He worshipped excessively. His social and work functioning were markedly impaired. This psychotic behaviour was preceded by an epileptic seizure (left focal becoming generalised), which the patient had about 8–10 hours before the psychotic excitement. After the seizure the patient had slept for 8–10 hours, and on awakening showed this abnormal behaviour.

A family history of an episodic mental illness (type not known due to inadequate information) was reported in a maternal uncle. The patient had no past history of any mental illness. The patient had had post-natal complications and had developed cyanosis at birth. Convulsions started in early childhood and were inadequately controlled by phenobarbitone (120 mg per day). His motor developmental milestones were delayed (walking and talking, for 4–5 years; bowel control, 7 years; self-care, dependent till 18 years). He could not cope with the studies and hence discontinued schooling after three years. Since then he has been working as a helper in the garden, under his father's supervision.

His mental state showed an unkempt appearance, restlessness, mannerisms, taking deep breaths, many times holding his abdomen. He had no confusion or disorientation. He would suddenly laugh loudly and inappropriately. A diagnosis of moderate mental retardation with epilepsy and post-ictal psychosis was made. The patient was prescribed haloperidol (10 mg), diazepam (10 mg), and diphenyl hydantoin (200 mg) daily, in addition to phenobarbitone (120 mg per day).

The patient reported two weeks later. His excitement had reduced, but he reported second- and third-person auditory hallucinations. He was convinced that he was pregnant and somebody was trying to harm him. He had a silly smile, and his talk was irrelevant only on occasions. He had no seizure and his sleep had improved. There was no disorientation or confusion. Haloperidol was increased to 15 mg per day because of continuing psychotic symptoms. A follow-up a month later showed that the psychosis had remitted. He showed no abnormal behaviour and had almost reached his pre-morbid level of functioning. The total duration of psychosis was six weeks. Mr A. felt embarrassed to talk about his abnormal belief (of being pregnant) and could not explain how or what had happened to him. The belief of being pregnant was not due to any abnormal sensations or in any way related to his auditory hallucinations. He confirmed that he had believed he was pregnant and he no longer believed so after treatment. His IQ was tested and found to be 42. There were no apparent disturbances in his relationship with his mother or any other family member.

Discussion

The number of recorded instances of delusions of pregnancy in men seems to be very small, and the possibility of a common psychodynamic link determining the content of the delusion has been mentioned in the cases reported earlier (Enoch *et al*, 1967). Jenkins *et al* (1962) speculated that in the case reported by them: "by carrying this baby in his stomach he was doing more than acting out a rebirth fantasy. He was playing both the role of the good bearing mother and the reborn self." Similar dynamic explanations involving the mother's attitude were offered in other cases of delusions of pregnancy. In the case presented here, no obvious disturbance of mother–child relationship was noted, but it is difficult to confirm or deny the role of such a factor. The psychosis in our case was characterised by excitement, auditory hallucinations, delusion of pregnancy and persecution, and inappropriate affect, following an epileptic attack. Mental retardation (IQ 42) and epilepsy (left focal, becoming generalised) are probably more important in this case in the development of the delusion of pregnancy. The delusion occurred in the post-ictal period and one possibility could be that the patient had misinterpreted bodily sensations during or following epileptic attack. It is necessary to note that he had reported the sensation of pressure on his chest, and any abnormal sensation in the abdomen could have been misinterpreted as a pregnancy, due to his intellectual handicap and post-ictal phenomenon. However, he had no disorientation or confusion. There is no mention of delusion of pregnancy in epileptic men with post-ictal psychosis in the available literature.

Organic factors seem to be implicated more than psychodynamic factors in most of the cases described. A common trend emerges when all the previous reported cases are examined. These had chronic organic brain syndrome (Baonville *et al*, 1935), delusion of infestation (where the role of vitamin deficiency and polyneuropathy is well known) (Alliez *et al*, 1956), general paresis of the insane (Alliez *et al*, 1956), post-encephalitic syndrome (Neveu & Boyer, 1950), and mental retardation with acute confusional state (Jenkins *et al*, 1962). The patient reported here had epilepsy and mental retardation, and the delusion developed in the post-ictal phase. The evidence is thus quite strong for organic brain damage playing a part in the development of delusion of pregnancy in men.

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Contents: Taking a good history/Repetition of parasuicide/Loss and theft/The use of propofol for anaesthesia during ECT/Sex chromosomes and psychosis/Elderly eccentrics/The Fear Questionnaire/Is globus hystericus?/Hospital suicides/Homo-erotomania/Violence in sleep: a further diagnostic consideration/Nosological problems/Chronic patients in acute wards/Admission trends/The mind-body problem/Psychological-mindedness and the alexithymia construct/Illicit drug use in strength athletes.

Taking a good history

SIR: Hare's paper (*Journal,* October 1988, **153,** 521–531) is one of the widest-ranging attempts so far to mount a coherent argument that schizophrenia is a recent disease which arose around 1800. Some of his evidence is extremely detailed, but we feel that many of his deductions are questionable, in the light of other historical information which may not be readily accessible to most psychiatrists. There is room here to deal with only a few.

Dr Hare mentions that descriptions of schizophrenia were rare before 1800, and suggests that some change "of a biological kind" occurred about that time, producing a new form of the illness. This, he postulates, might have been the disorder known as 'adolescent insanity', which he argues to have been rare at the beginning and common at the end of the 19th century. In support of this he quotes Harper (1789).

However, Harper's experience of insanity in Britain must be in doubt, as he seems to have been an army surgeon serving overseas. Moreover, his statement, quoted by Hare, that it was "well known that young people are hardly ever liable to insanity, and that the attack of this malady seldom happens until an advanced period of life" is contradicted by the more reliable evidence of John Haslam, apothecary to Bethlem Hospital (Haslam, 1809), citing the statistics for Bethlem between 1784 and 1794. Out of 1664 admissions, 7% were aged between 10 and 20, 29% between 20 and 30, 32% between 30 and 40, 22% between 40 and 50, 8% between 50 and 60, and 2% between 60 and 70. Admissions to the Bicêtre for the same period show only marginal differences.

It is unclear from Dr Hare's paper whether the 'recency' hypothesis refers to schizophrenia as a whole, or to a particular subtype like the 'early onset' variety to which he refers. Appealing to different forms of a disease at different stages of an argument about its history serves to allow an infinite flexibility in the theory, and perhaps this and other features tend to render the recency hypothesis unfalsifiable.

Even if the 'subtype' issue is allowed into the debate, however, there is good evidence that it does not help the hypothesis it is supposed to serve. Statistics derived from primary sources indicate that 'adolescent insanity' was not on the increase, although Hare suggests that its growth was an important feature of the 19th century. Wilkins (1987) looked specifically at admission rates to Bethlem during this era for age groups which he considered most at risk for developing schizophrenia. His figures reveal no discernible trend: for example, the numbers of admissions for children and teenagers for 1840–1849 was 181, and for 1890–1899 it was 107 (and incidentally, it was 113 between 1784 and 1794, when the total intake was far smaller).

Dr Hare argues that descriptions of recognisably schizophrenic symptoms are difficult to find at the beginning of the 19th century, and that the major signs, "thought disorder, flatness of affect, loss of initiative – are not only hard to assess, but in the absence of an accepted terminology would be hard to describe". This is, again, to ignore the work of Haslam, one of the few authors on insanity at this time who had much direct experience of the subject. "... there is a form of insanity which occurs in young persons ... The sensibility appears to be considerably blunted; they do not bear the same affection towards their parents and relations; they become unfeeling to kindness, and careless of reproof ... As their apathy increases they are negligent of their dress, and inattentive to personal cleanliness. Frequently they seem to experience transient impulses of passion, but these have no source in sentiment; the tears which trickle down at one time, are as unmeaning as the loud laugh which succeeds them". (Haslam, 1809).

Haslam also refers to the frequency of auditory hallucinations among the insane, and elsewhere he devotes an entire book to the study of a patient admitted to Bethlem in 1797 with what appear to be classic symptoms of schizophrenic thought disorder (Haslam, 1810). What is important about all these descriptions of schizophrenia-like symptoms is that he writes of them as though they were nothing new: indeed, as though they were so common, obvious, and typical that it is scarcely surprising that most authors found them hardly worth mentioning, at a time before interest in phenomenology had developed, and when they had few opportunities for observation anyway.

The purpose of the evidence presented here is not to disprove the 'recency' hypothesis: our aim is rather to suggest that the historical reasoning it relies on is often dubious. The importance of Dr Hare's work is to raise issues which are important to modern psychiatry, while demonstrating how essential historical knowledge is to the debate. The history of psychiatry is too important to be left entirely to historians ignorant of clinical issues, or psychiatrists unqualified to evaluate historical evidence. As there can be few practitioners trained in both disciplines, we would plead for more active co-operation between the two.

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Repetition of parasuicide

Sir: We studied the repetition of parasuicide in Edinburgh in the period 1980–1981 (Wilkinson & Smeeton, 1987), and so read with interest the report by Kreitman & Casey (*Journal*, December 1988, 792–800). We are puzzled as to why the authors based their categories of 'first-evers', 'minor repeaters' and 'grand repeaters' on the individual lifetime history of parasuicidal episodes. Given a stable pattern of parasuicide with respect to each cohort, more major repeaters are to be expected among older individuals, since they have been at longer risk of having an episode. This observation can be seen in Table II of their paper, up to the age of 34. Results for different age-groups would be made more comparable by assessing the patient on a recent fixed period of time (say two years), as in our recent study of parasuicide repetition (Smeeton & Wilkinson, 1988a).

Incidently, the fact that there are relatively few major repeaters over 35 years of age seems to indicate that these individuals had episodes of parasuicide *much* less frequently in their youth than the present generation of young repeaters. In order to verify this trend one would have to check parasuicide records categorised by age over at least 30 years.

On the subject of prediction, we found that major repeaters (five or more episodes in 2 years) could be sub-divided into those with clustered and those with chronic patterns of parasuicides. Prediction should be much easier for those with a clustered pattern, since once one parasuicide is observed, a series will probably follow in the near future. In another type of clustering, episodes may occur around the same dates in consecutive years (Smeeton & Wilkinson, 1988b). It would be particularly interesting to see how clinical and social problems are related in time to clusters of episodes.

With the possibility of the clustering of episodes in mind, the lifetime history seems a rather crude measure of current needs. It may be that some patients with a large number of prior episodes (Drs Kreitman & Casey's major repeaters) are currently experiencing an untroubled period. Conversely, some of their minor repeaters may be commencing a period of frequent repetition and may be experiencing problems which are far from minor.

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SIR: Mr Smeeton and Dr Wilkinson ask why we categorised our patients on the basis of their lifetime history. The answer is that this method seemed to us the simplest, and to rest on no assumptions about patterns of repetition. Their proposal to classify patients solely by the number of episodes in the preceding two years implies that such clustering is a salient and consistent feature of repetition, and while there is some interesting evidence that this might be so, we do not think that at present it provides a secure basis for classification. Moreover, contrary to another of their suggestions, it turns out not to be true that the number of parasuicidal episodes increases linearly with age simply as a function of increased time at risk. The older patients in our series show a different pattern of parasuicide from younger subjects; they are predominantly first-ever admissions, and major repetition is distinctly rare. Our present view is that such patients are quite a different group from the younger ones, and probably reflect differences both in psychopathology and in social contex.

Mr Smeeton and Dr Wilkinson raise the possibility of a birth cohort effect for parasuicide, much as proposed some years ago by Alderson (1974). They also indicate that formally testing such a model is scarcely feasible. But for what it is worth, we have found in our own data, which extend back to 1968, that the frequency of a prior episode in relation to age has constantly been much as reported in our recent paper. There is thus little support for a cohort effect. Alderson (1985) has come to the same conclusion for England and Wales.

Finally, they suggest the use of cluster patterns as a prognostic indicator among the major repeaters, referring to their own studies and work by others. This approach is eminently worth pursuing, but can only be applied to a small minority of all patients – less than 3% in their 1987 paper. Most repetitions will be generated by the much larger group of first-ever and 'minor' repeaters. Even for the major repeaters it would be unwise to base predictions solely on the past history of parasuicide and to ignore the many other aids to prognosis that are now available. Indeed, if we understand them correctly, Mr Smeeton and Dr Wilkinson themselves appear to recognise this point. At present there is no substitute for comprehensive psychiatric and social assessment in any attempt at prediction.

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Loss and theft

SIR: In Fishbairn's letter about shoplifting (*Journal,* June 1988, **152,** 845–846), he wrote about risk-taking having an antidepressant effect and wondered if this was the mechanism behind shoplifting. In some 90 cases which I have studied, the event which always precipitated the risk-taking behaviour was a loss, or a threatened loss, of a significant other held in a symbiotic relationship with the self, which was experienced as a catastrophe and necessitated that they were caught in the act. This behaviour is similar to the all-or-nothing mode of the narcissistic personality, and ensures that someone cares when it was felt that nobody cared at all.

An illustration can be seen in the behaviour of a tertiary-educated woman who had been a compulsive shoplifter and had been seen for a year for twice-a-week psychotherapy, and had not shoplifted over that period. In a session it was suggested by the therapist that consideration could be entertained to work towards the ending of therapy. An hour later I was rung by the police to say that she had been caught shoplifting and that her mental state was such that they thought she needed hospitalisation.

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The use of propofol for anaesthesia during ECT

SIR: Rands (*Journal,* January 1989, **154,** 125) is correct to draw attention to the adverse effect of propofol anaesthesia on seizure duration during electroconvulsive therapy (ECT). In a study involving 25 patients we observed that the use of methohexitone produced a median (QD) seizure duration of 33.0 (7.8) s, whereas the use of propofol significantly reduced this to 19.0 (9.0) s ($P < 0.01$) (Simpson *et al,* 1988). We concluded that propofol was not an appropriate agent for ECT anaesthesia, and that methohexitone should remain the standard agent. Since then, two other studies have shown that both observed seizures (Rouse, 1988) and cerebral electrical seizure activity (Dwyer *et al,* 1988) are attenuated by propofol.

In view of these findings we feel that the use of propofol anaesthesia for ECT should be discouraged, despite the obvious advantages of the drug for brief anaesthesia.

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Sex chromosomes and psychosis

SIR: The paper by Crow (*Journal*, November 1988, **153**, 675–683) raises many interesting points. He suggests that there is a pseudoautosomal locus on sex chromosomes for psychosis, but fails to mention whether the gene is dominant or recessive. We presume he has a dominant gene in mind, because one would not expect to find vertical concordance of sex with a recessive gene. The following possibilities occur to us for genes on the X or Y (underlining indicates presence of psychosis gene): paternal inheritance, (a) $X\underline{Y} \times XX = XX, X\underline{Y}, X\underline{Y}$ ... (b) $\underline{X}Y \times XX = \underline{X}X, \underline{X}X, XY$ ...; maternal inheritance, (c) $\underline{X}X \times XY = \underline{X}Y, \underline{X}X$ ....

Dr Crow presents data to show same-sex concordance in sibs in schizophrenia, and has evidence for paternal transmission. This is consistent with (a) and (b). An excess of father-son over father-daughter transmission leads him to suggest a locus for schizophrenia with preferential mutation on the Y chromosome (situation (a)). Sib sex concordance is quoted for affective illnesses, as are excess of female-female sib pairs and a deficit of father-son transmission. These observations lead him to suggest preferential mutation on the X chromosome for affective illnesses (situation (b)). The lack of mother-daughter and mother-son difference is consistent with (c). We think it is an interesting hypothesis that explains certain cases of psychosis, but the model becomes strained if it attempts to account for all the epidemiological data. When Dr Crow tries to explain the greater severity in male schizophrenics he is referring to an X-linked semi-dominant model. We would also expect an excess of male schizophrenics and male-male pairs if we accept his model of preferential mutation on the Y chromosome for schizophrenia. He has attempted to explain these anomalies, but most importantly has failed to offer any evidence for paternal inheritance in affective illnesses which would be expected with a sex concordance in sibs. How does one explain the lack of same – sex concordance in the other sibling pairs? We would like to suggest that the reason may be genetic heterogeneity as well as variable penetrance.

A possible problem associated with genes in this region is the small size of the segment. Chromosomally, it cannot be larger than about 0.5% of the genome. Furthermore, the particular region that would give the exact concordance of sex must be a small segment on the border between the pseudoautosomal region and the region of the X- and Y-linked genes, because the obligatory crossover must occur proximally to the genes in question most of the time (>80%) for the concordance to be observed. Thus the total region in question must be less than 0.1% of the genome and possibly even smaller. This does not mean that the gene cannot be in this region, but it does mean that the possibility can be checked easily.

If we accept heterogeneity as a possibility, a case for X- and Y-linked genes can be made to give most types of concordance. Several types of sex-linked inheritance can be distinguished:

(a) X-linked lethals (often called sex-linked dominant): these are always passed on maternally, and would produce concordance of mother-daughter and sisters, as well as a deficiency of affected males, and a distorted sex ratio (2:1).
(b) X-linked true dominants: where male and female are similarly affected, would produce sister concordance from paternal transmission and no concordance from maternally affected individuals.
(c) X-linked semidominants: paternally passed on, genes would produce concordance of mild cases in the sisters and no affected sons. Maternally transmitted genes would show concordance of mild cases between the sisters and the mother, and concordance of severe cases between brothers.
(d) X-linked recessives: would produce, if passed on from the mother, concordant brothers; if passed on paternally, no affected individuals would be produced.
(e) Y-linked genes: always passed on paternally, and concordance is complete between all males.

We realise that no single hypothesis will account for all the data. However, it is possible that a gene or some genes for psychosis could be controlled by sex-linked factors and produce various types of concordance. Muscular dystrophy in man not only has allelic types of varying severity located on Xp21, but also there are autosomal loci with similar phenotype (McKusick, 1988). So it is by no means impossible that one phenotype can be produced by several loci or a single locus with multiple alleles. Thus, the question of heterogeneity must not be forgotten. There is already experimental evidence for it (*Lancet*, 1987, 1988), but in a previous communication Dr Crow (1987) found it difficult to accept. We would suggest that pseudoautosomal or Y-linkage might be found if selected cases of father-son transmission were investigated, and that the X-linkage for the long arm already found in some families with affective disorders might be associated with those cases showing sex concordance.

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McKusick, V. A. (1988) *Mendelian Inheritance in Man*. Baltimore and London: The Johns Hopkins University Press.

Sir: Certainly the possibility of heterogeneity must not be forgotten. Drs Schiwach & Crocker follow in the confident footsteps of the Lancet leader writer (1987) and Lander (1988) in concluding that it has already been established. But neither must it be too readily conceded. Occam's razor – that the simplest viable solution is to be preferred – is a powerful scientific principle.

The pseudoautosomal hypothesis arose from the counter-Kraepelinian notion that the psychoses are distributed along a continuum (Crow, 1986) rather than existing as two discrete entities. As the Lancet leader pointed out, if psychosis is sometimes sex-linked (e.g. in some affective disorders) and sometimes not, it appears that heterogeneity must be accepted. In resisting that conclusion I was forced to consider a pseudoautosomal locus (Crow, 1987), and having done so realised that it could account for same-sex concordance. This finding has been known, although neglected, in schizophrenia for many years. As far as I am aware it has not been commented on in the affective disorders; but it is present here also (Crow, 1988). The prediction of the pseudoautosomal theory is that it originates when the disease is inherited from the father. This has recently been confirmed in the case of schizophrenia (Crow *et al*, 1989), but not yet tested in the affective disorders.

Drs Shiwach & Crocker's explanation of same-sex concordance on the basis of pseudoautosomal inheritance is misleading in one respect. They are correct in supposing that it will arise when the gene is inherited from the father and not from the mother. The complexity arises from recombination between X and Y chromosomes in male meiosis. As a result of the single crossover that takes place somewhere within the pseudoautosomal region, a gradient of sex linkage exists from the pseudoautosomal limit (where there is sex linkage) to the short arm telomere where there is 50% crossover (i.e. sex linkage is absent). Same sex concordance will arise providing the crossover in either sibling has not occurred proximal to the putative locus. With a locus centromeric in the region (i.e. close to the limit) crossing over will generally be distal, and same-sex concordance will be prominent. With a locus at the telomere (with 50% crossover), concordance by sex will be absent. Therefore the size of the effect gives an indication of the location of the gene – the bigger the effect (assuming that it originates in paternal transmission), the closer the gene is likely to be to the border between pseudoautosomal and sex-specific regions.

But Drs Shiwach & Crocker state that "the obligatory crossover must occur proximally" (perhaps they mean distally) "to the genes in question most of the time (>80%) for the concordance to be observed". While it is true that same-sex concordance could arise as a result of proximal crossover in both siblings, because the rate of crossover in each male meiosis even at the telomere does not exceed 50% (only one of the two chromatids that make up each chromosome is subject to recombination) this will be an infrequent event. Whatever their meaning, Drs Shiwach & Crocker's conclusion is the same as mine – the locus should be close to the border between pseudoautosomal and sex-specific regions.

Drs Shiwach & Crocker draw attention to a number of other ways in which same-sex concordance might arise. Most if not all predict a sex difference such as is absent in schizophrenia and probably also in bipolar affective illness. Therefore, no one of these mechanisms provides a general explanation for transmission of psychosis; nor can they account for concordance by sex except in an unspecified subgroup of cases. A pseudoautosomal locus is compatible with equality of incidence in the two sexes, although it cannot readily explain certain other sex differences, e.g. earlier onset of schizophrenia in males, the sex ratio in depression. I agree that my attempts to modify the theory in this respect are not entirely successful; but I do not feel compelled to adopt another explanation of concordance by sex while a pseudoautosomal hypothesis still gives some promise of a more general explanation and one which may be applicable to both schizophrenia and affective disorder. Nor am I yet convinced that any of the linkage findings so far provide compelling evidence that genetic loci for psychotic illness are present either on the autosomes or on the long arm of the X. I believe that the problems in the field of psychiatric disorder are such that linkage findings can be regarded as definitive only when there is substantial agreement between two and preferably more independent studies.

For these reasons, encouraged by the counsel of William of Occam (and perhaps also by the example of King Canute) I will adhere to a unitary concept until the tide of heterogeneity flows with greater force. I predict that the genetics of psychosis can be accounted for by changes within the pseudoautosomal region – a one thousandth part of the human genome – and that the findings elsewhere may prove to be irrelevant.

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Elderly eccentrics

SIR: Tantam (*Journal*, December 1988, **153**, 777–782) unfortunately tells us nothing of people aged over 65 years who are apparently eccentric and/or socially isolated.

While there are few (if any) epidemiological data about these subjects, Clark's evocative label 'Diogenes' syndrome' (Clark *et al*, 1975) is immediately recognisable by geriatricians and geropsychiatrists in spite of historical criticism (Cybulska & Rucinski, 1986). When the article by Clark *et al*, appeared, James Williamson, then Professor of Geriatric Medicine in the University of Liverpool, immediately coined the term 'pseudo-Diogenes' syndrome'. By this he meant that the antisocial rejection of help and associated squalor result from a dementing process, whereas Clark reported that all his patients who were formally tested were cognitively competent with "no gross deviation of personality". The distinction continues to be important, particularly when professional carers are asked to act *in loco parentis* for these patients.

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The fear questionnaire

SIR: The recent paper by van Zuuren (*Journal*, November 1988, **153**, 659–662) on construct and discriminant validity, reliability, and layout of the Fear Questionnaire (FQ) with agoraphobic, socially phobic and simple phobic subjects, while it could have contributed to the utility of the instrument for clinical and research purposes, is rampant with errors of omission and is misleading on specific points.

Firstly, in a previous version of the paper (van Zuuren, unpublished), the author noted that the phobics were diagnosed by an experienced psychiatrist, while for the purpose of research in a further stage, the written reports of the clinical interviews that were provided by the psychiatrist were used by a researcher for assigning each patient to any of six phobic categories (three more than included in DSM-III). Each category was concerned with the types of feared and avoided situations. As to agoraphobia, the author noted that its categorisation was based on the researcher's focus on fears of being in public, anonymous situations, and/or being alone. DSM-III requires two additional criteria. In the *Journal* article, however, Dr van Zuuren points out that the patients were categorised according to DSM-III criteria. Clearly, her claim that DSM-III criteria and the guidelines used in her study overlapped to a large extent (van Zuuren, unpublished) can not be upheld. Moreover, the validity of the categorisation used could be questioned on the basis of the lack of the following information: (a) the quality and reliability of the written reports of the clinical interviews, (b) the degree of match between diagnostic ratings provided by the psychiatrist and those returned by the researcher, (c) the inter-rater reliabilities corrected for chance agreement (weighted kappas) for ratings of different researchers for each category of phobia, and (d) the basis for using more than the three categories of phobic subtypes that are described in DSM–III and, related herewith, how the six categories used by the author relate to those given in DSM–III (an alternative categorisation to the one used by the author might produce findings on the discriminatory power of the FQ that differ from those yielded in her study).

Secondly, Dr van Zuuren states that for determining the construct validity of the FQ, its dimensions (e.g. agoraphobia and anxiety-depression) were correlated with well-known and accepted questionnaire measures of neuroticism and social anxiety. In addition to both measures being clearly Dutch in nature – which makes them less internationally well-known and accepted than is implied by the author – the reader is not informed about their reliability and validity with phobic samples. The lack of reliability data for phobic patients on both measures is especially distressing, since such findings are important for making corrections for attenuation (Nunnally, 1978) to the original correlations feasible. In addition, the study-specific α-reliabilities for the FQ subscales were not reported; only their ranges were given. This omission limits our understanding of the 'true' magnitudes of the relevant validity coefficients. The lack of a statistically significant association between the FQ agoraphobia subscale and neuroticism, as reported by the author for male phobics, while representing a negative validity finding (not noted by the author) in the light of findings from several studies showing at least a moderate relationship (e.g. Chambless, 1982), might be due to either low internal consistency of the latter measure for the sample under consideration, small sample size, or both.

Thirdly, the discriminatory power of the FQ was determined by comparing DSM–III phobic patient groups with each other and claimed by the author to be acceptable. However, a normal control group specifically designed for the study was clearly lacking, which limits the conclusions that can be drawn. In actual fact, the patient groups were contrasted with American normative data (normal adults), which is quite a remarkable practice since the patients were all Dutch. There are several problems here: (a) no information was provided with respect to the comparability of the patient groups on background variables that affect the self-report of fears, such as age and educational level (cf. Farley *et al*, 1981); (b) sample sizes were quite small for specific comparisons ($n<10$); (c) there are as yet no published data indicating that the FQ fear components are invariant across samples comprising the different phobic subtypes – a prerequisite for performing sound comparisons between groups in terms of descriptive statistics (e.g. Derogatis & Cleary, 1977); (d) neither are there any data yet available that show the FQ dimensions to be constant across comparable American and Dutch samples (comparable in terms of background factors and type); and (e) due to baseline differences between national/cultural groups on many different self-report state and trait measures of psychological functioning (Triandis & Draguns, 1980), the results of comparisons between Dutch patients and American normals should not and can not be taken seriously.

Fourthly, and finally, different cut-off scores were suggested by the author for determining phobic cases, the serious omission with respect to this point being that the validity of such scores has not been established. It is of prime importance to have such information first, for example by putting the cut-off scores against an objective external standard (e.g. a reliable and valid interview schedule), so as to provide relevant findings relating to base rate, misclassification rate, sensitivity, and specificity.

By adding questionable findings and suggestions with regards to validity and utility of the FQ to the research literature, the study considered here teaches us little about the potentials and psychometric properties of the instrument. Rather, it illustrates the relative ease with which unjustified and naive conclusions are drawn in this area of research. After practically 25 years of research with self-report fear inventories, their users still know little about their psychometric merits.

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Triandis, H. C. & Draguns, J. G. (eds) (1980) *Handbook of Cross-Cultural Psychology, Volume 6: Psychopathology*. Boston, Ma: Allyn and Bacon.

Sir: In my article I tried to shed some light on the FQ's psychometric properties. The study is rather unique in providing and analysing data, not of subclinical phobics, but of subtypes of phobic patients. The number of subjects amounts to 143, which took years of data collection.

Dr Arrindell's first comments concern the classification of phobic subtypes, which is obviously a difficult task – this is why instruments such as the FQ have to be developed in the first place. The more elaborate criteria mentioned in the unpublished report I sent him at an earlier stage attempted to guard against too much heterogeneity within each DSM–III category. This was done by introducing the category of multiple phobia (this category was even further differentiated in the original version). Such an extension will not surprise those who have clinical experience with phobic patients. Moreover, including this category is fair to the FQ: one cannot expect a questionnaire to differentiate better than reality does. Also, taking the diagnostic options of the FQ into account, we added the category of death/illness phobia. These decisions are clearly stated in the published text, so that there can be no misunderstanding about their implications.

Secondly, in order to be concise I confined the results section on the internal consistencies (αs) of the subscales to the most informative data (p. 660). It is clear that the complete data can be obtained on request, and surely Dr Arrindell found them in the unpublished report.

With regard to the neuroticism and social anxiety scales used, I do not see why these measures, "being clearly Dutch in nature", should be discredited. Obviously, we cannot confront Dutch subjects with English tests. Moreover, the scales used are among the best we have in The Netherlands and they meet internationally accepted standards.

Contrary to Dr Arrindell's statement, the low correlation ($r = -0.06$) between neuroticism and the agoraphobia subscale in phobic men *is* noticed in the text – with the predicate "rather surprisingly" (p. 660). He is right in pointing out that as long as the internal consistency of the neuroticism scale in the present sample is not assessed, the extent to which internal consistency may account for the low correlation remains unclear. Other data, however, (Luteijn, 1979) suggest that low internal consistency is not very likely. Using an unweighted scoring method with a slightly different set of items, Luteijn found a Cronbach's $\alpha = 0.90$ for Dutch psychiatric patients on the neuroticism scale.

Furthermore, the moderate relationship between neuroticism and severity of agoraphobic symptomatology reported by Chambless (1981) does not necessarily contradict our results. Dr Arrindell mentions neither the relevant αs, nor the proportion of women in the sample (for phobic women in our sample $r = 0.29$, $P < 0.02$; p. 660).

In order to obtain a complete picture of the discriminatory power of the FQ, several control groups are needed, such as normals, subclinical phobics, and other patient groups (see also the Discussion section). The absence of such groups in the present study, however, does not invalidate the comparisons that have been made among phobic subtypes.

To indicate the scoring of a normal group, I referred to the results Mizes & Crawford obtained with American normal adults (p. 661). Here, Dr Arrindell reasons *as if* their subjects had been included in the design of the present study, *as if* differences between their scores and those of our subjects had been tested statistically, and *as if* far-reaching conclusions had been drawn. In fact, only a global comparison without any pretension is made. The five considerations pertaining to ideal control groups he enumerates should not prohibit examination of the few – less than perfect – data available. A tentative conclusion can always be replaced and better understood in the light of subsequent research. This is the way science proceeds.

The last point of criticism can be met in the same vein. The cut-off scores suggested in the Discussion are the best we can give on basis of the present data. It is beyond the scope of the study to settle them more definitively.

In conclusion, then, I consider the present study as one in a chain of endeavours to obtain a truthful and complete picture of a specific field of inquiry. In these endeavours, statistical methods should be used as tools for discovering meaningful relationships, not as rules leading to a preoccupation with numbers at the cost of a profound interest in the subject matter.

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Is globus hystericus?

SIR: The Journal Club at this hospital met recently to discuss 'Is globus hystericus?' by Wilson *et al* (*Journal*, September 1988, **153**, 335–339). The exercise seemed to offer considerable educational rewards, which other readers may wish to share if they have not already done so. An initial difficulty was that the promisingly quizzical title of the piece obscured its evident lack of scientific objectives beyond "the use of psychological inventories in globus patients". Its potential value paled further as no adequate description was to be found of how the patients included in the study were selected for it, let alone of how they compared with co-attenders at the same department who were not. The reasons for choosing the instruments used, the GHQ and the EPI, were not given; the choice seemed inadequate for most purposes, given the well-known problems of interpretation of the former in the context of physical illness, and the lack of discriminatory value exhibited by the EPI in the only comparable psychological study of hysteria the authors quote. (The authors hardly increase confidence in their objectivity when they opine, in anticipation of criticism of the GHQ, that "we do not agree . . . that most cases of globus have a physical basis"). The interpretations they place on their questionnaire findings, that they "support the inclusion of conversion disorder with dysthymic disorders", prompted much surprise, the study being notable for the absence of any specific measure of affective symptomatology, or any independent attempt at psychiatric diagnosis of its sample.

We appreciate that the publication of any study that fails, as this one does, to acknowledge related psychiatric research (e.g. previous studies of other discrete hysterical syndromes such as pseudoseizures), and whose own design is flawed, may inspire more satisfactory successors. However, our meeting did feel that the value of such a study is otherwise limited, and that it should not be taken as a model for others.

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SIR: How striking that six workers at the National Hospitals for Nervous Diseases (NHND) should take exception to one of the few empirical reports on the personalities of globus patients. We selected the Eysenck Personality Inventory, the best-known and best-validated personality test in Britain – long percieved by its author, Hans Eysenck, to distinguish individuals suffering from hysterical disorders. We reported simply that female globus patients were markedly neurotic and introverted and that our small sample of male patients were decisively low in emotionality.

The study had clear scientific objectives beyond the use of psychological questionnaires – indeed, these are stated in the first few lines of the abstract. The patients were investigated with a wide range of physical tests – radiology, haematology, endoscopy, and specialised tests of oesophagogastric function. That these were somehow overlooked by your correspondents from the NHND brings out an important point about globus pharyngis, namely that the background literature, current aetiological theories, and clinical experience of the condition are, with a few exceptions, confined to departments of otolaryngology.

The patients were diagnosed using the standard clinical criteria for globus, and they were consecutive attenders at the globus clinic in our ENT department. Otherwise they were unselected. We accept that the data from this exploratory psychological assessment, which was performed in conjunction with extensive physical investigations, would have benefited from the inclusion of an ENT control group. We were, however, able to compare our patients with matched British norms, such as are furnished currently by no other form of personality assessments, and to show an unexpected and interesting result.

Our statement of disbelief in the physical basis of globus was not a subjective opinion intended to deflect criticism of GHQ scores. Rather, it was our conclusion after the negative results of our extensive physical investigations. These are reported in the text and are, as also stated in the paper, published elsewhere.

We are criticised for suggesting, on the basis of the globus model, that conversion disorder be included within the dysthymic group. Readers beyond the first half sentence of this paragraph will see that the term dysthymic was used in the way that Eysenck has used it for over 40 years – to refer to a group of neurotic disorders where patients' personalities tend to be introverted and high on neuroticism. Nevertheless, the workers from NHND appear to be unaware of the finding that neuroticism scores are strongly predictive of mood fluctuations (particularly dysthymic swings) over time (Williams, 1981).

Our reference list (44 items) does contain recent reviews of conversion disorder and will be adequate for most readers of a publication of this nature. We stated on the first page of our text our reasons for considering globus to be different from disorders such as pseudoseizures.

It remains our opinion that globus might make a good model for conversion disorder. The results of our preliminary study have encouraged us to continue our study of psychological factors in globus. A report, in preparation, of a substantial number of patients, including an ENT control group, uses questionnaires designed to index psychoneurotic disorder and attempts to replicate our previous results on the personality traits of globus patients.

We agree with the workers from NHND that journal clubs can be educationally rewarding. Sometimes, however, the joint perusal of a document can lead to errors in understanding.

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Hospital suicides

Sir: During our psychiatric training, it has been our combined experience that when a patient commits suicide, the responsible team responds with a mixture of sorrow, guilt, embarrassment, and concern about possible litigation; there is little open discussion.

In our training, much attention is given to learning about known risk factors for suicide. However, despite an extensive literature, assessing suicide risk remains an imprecise art and virtually all psychiatrists recognise that despite their best efforts, some patients will successfully take their own lives.

It seems to us strange that emphasis is placed on learning about the theoretical aspects of assessment of suicidal risk, but that when a suicide does occur, the absence of ensuing discussion severely hampers the learning of practical lessons.

We believe that a completed suicide in a psychiatric patient is an extremely valuable opportunity from which lessons may be learnt for the benefit of future patients. It is our belief that formal discussion of such cases would have several benefits: firstly, and most importantly, it would help the responsible team and other staff to learn from the case: secondly, it would reduce unhelpful speculation; thirdly, if conducted sensitively, it would reduce, rather than increase, the anxieties of involved professionals; and fourthly, it could facilitate later discussion with bereaved relatives.

In medicine and surgery it is standard practice to hold post-mortem review of 'difficult' cases, with formal discussions of findings in the light of clinical presentation and interventions. We are not aware of this practice in psychiatry, but would be keen to learn of its existence and of the opinions of those who have experienced it.

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Sir: Goh *et al* (*Journal*, February 1989, **154**, 247–249) draw attention to the special features of suicide by psychiatric day and in-patients, and highlighted the importance of factors that related not only to the patient's illness but also to the immediate ward environment. Using the Edinburgh Suicide Case Register, I recently identified and reviewed the case notes of psychiatric in-patients who committed suicide in the Royal Edinburgh Hospital between 1977 and 1985. There were 29 such cases, and this population shared many of the characteristics of that described by Goh *et al.* However, in the Edinburgh survey there was an increased proportion of females, and the diagnoses of neurosis, personality disorder, and adjustment reaction were more common than in the Birmingham study. Also, over half had a past history of deliberate self-harm.

The notion of the high-risk patient can be described with reference to the characteristics of those who complete suicide, but it is more difficult to predict from patient characteristics which ones actually go on to commit suicide. Pokorny (1983) identified patient characteristics on admission in an attempt to predict which ones would later kill themselves, without success. Thus, it is particularly relevant to consider what local environmental factors influence suicide, as such factors may lend themselves more liable to change. Local ward layout is of obvious importance – such as the types of windows, window locks, and bathroom arrangements. In the Edinburgh study, means of suicide ranged from hanging by a bathrobe cord in the ward toilet area to jumping off the Forth Road Bridge.

Some studies of in-patient suicide have commented on staff factors which may influence the risk of patient suicide – from a case-note review it is particularly apparent that in some cases there are claims for negligence against the hospital or medical/nursing staff. Although the impact on staff is not usually so extreme or direct, the way in which staff respond and deal with the aftermath of a suicide at ward level is a relatively unexplored area. A prospective descriptive study of how different teams and wards deal with suicide would be of value. Going on from this is the question of how one suicide influences the other patients and whether it makes further suicides more likely.

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POKORNY, A. D. (1983) Prediction of suicide in psychiatric patients. *Archives of General Psychiatry*, **40**, 249–257.

Homo-erotomania

SIR: Two cases of homo-erotomania were recently reported by Dunlop (*Journal*, December 1988, **153**, 830–833), although several have already appeared. Fretet (1937) discussed an alcoholic male and Peterson & Davis (1985) a schizophrenic man with this variant. Lovett Doust & Christie (1978) make it clear that two of the eight cases in their series had homoerotic delusions: patient 2, with a cortisone-precipitated (affective) psychosis and increased alpha activity over the right hemisphere, believed an older married woman was in love with her; patient 6, whose imagined "calls" from a former male lover were triggered by alcohol ingestion, also had a son who believed he was being sexually pursued by another man. A schizoaffective woman had a possible prior homo-erotomanic episode (Signer & Isbister, 1987), and there are reports of two bipolar women, one (with left temporal lobal epilepsy) (Signer & Cummings, 1987) who had exclusive homo-erotomania, and another who had one prominent homo-erotic episode mixed in among several hetero-erotomanic ones (Bastie, 1975). Fretet (1937) mentioned a female homo-erotomania in passing.

A vast majority of cases show the features of an 'exalted' or excited state that serves as the marker for severe mood disorder, usually mania or psychotic depression. Almost all patients with erotomania become involved with the legal system because of their relentless pursuit of the object of their delusion, a classic feature of the 'psychoses passionnelles'; meeting or confrontation does not ameliorate the condition because of the cognitive distortions of psychosis.

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Violence in sleep: a further diagnostic consideration

SIR: Scott (*Journal*, November 1988, **153**, 692) has failed to mention a recently described sleep disorder which should be included in the differential diagnosis of sleepwalking and night terrors. This is a rapid eye movement sleep behaviour disorder (REM behaviour disorder) as described by Schenck *et al* (1986). This parasomnia is characterised by loss of the normal atonia accompanying the REM sleep stage, with the emergence of violent behaviours such as punching, kicking, and leaping from bed. Dreams are often portrayed as having been extremely vivid. The authors describe one patient who attempted to strangle his wife while dreaming of fending off a mauling bear.

Schenck *et al* (1988) characterised a group of 33 such patients with a mean age at presentation of 65.7 years, mean age of onset 55.5 years, 94% male, 24% with psychopathology, and 30% with neurological disorders (various CNS vascular and degenerative disorders). The polysomnogram was diagnostic in 100% of the cases, with loss of REM atonia and emergence of significant behaviour during REM sleep. Significant improvement was seen in 90.6% of these cases with the use of clonazepam (0.25–2.0 mg at bedtime).

This human sleep disorder is similar to behaviour which can be experimentally induced in cats by making a lesion in the locus coeruleus area of the pons (Jouvet & Delorme, 1965). Cats then demonstrate "REM without atonia" and are seen to manifest various stalking and pouncing behaviours during electroencephalographically recorded REM sleep.

The case described by Scott is obviously complex, with many diagnostic possibilities aside from the REM behaviour disorder. Once these are identified, the polysomnographic study of sleep is extremely useful in reaching the correct diagnosis.

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Nosological problems

Sir: Hamilton (*Journal*, February 1989, **154**, 201–206) draws our attention to an important area of nosological deficit. Several recent articles have also highlighted the anxiety-depression overlap, some using cluster analysis to display how poorly both the ICD and DSM classificatory systems apply to the group of symptoms which patients suffer.

Davidson (1988) and Blazer *et al.* (1988) have independently taken the process one step further, using graded membership analysis to differentiate system clusters which form possible sub-categories of anxiety neurosis and depressive illness. Each has suggested five categories – Davidson's projection being slightly more ambitious, as he also suggests that these categories predict treatment response and prognosis to some extent.

A good classificatory system must have general applicability to the clinical population under study, and should display continuity in the form of future symptom expression. Our current situation of re-emphasising these important nosological problems has become rather static, and we must look to the future. The potential sub-categories generated by statistical methods need to be applied in large clinical studies to demonstrate whether they have any role to play in achieving much-needed improvements.

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Chronic patients in acute wards

Sir: Simpson *et al* (*Journal*, January 1989, **154**, 77–82) drew our attention to some of the problems experienced by chronically mentally ill patients on acute District General Hospital wards. We recently surveyed the long-stay general psychiatric population (in-patients for more than 1 year) of Liverpool district (catchment population 400 000). We found that 16% (32 patients) were on admission wards. This proportion is alarming, as the district has been relatively well supplied with long-stay beds until recently.

Limited space, social facilities and occupational facilities are some of the factors which make admission wards unsuitable for the chronic severely mentally ill. However, the implications for the acute psychiatric services must also be considered. The new long-stay population are a major determinant of bed throughput on admission wards (Royal College of Psychiatrists, 1988). Therefore, inadequate provision of services for the chronically ill will have implications for the functioning of the acute services, as well as for the quality of life of this group of patients.

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Royal College of Psychiatrists (1988) *Psychiatric Beds and Resources: Factors Influencing Bed Use and Service Planning. Report of a Working Party of the Social and Community section of the Royal College of Psychiatrists*. London: Gaskell.

Admission trends

SIR: The effect of the growth of general-practice-based psychiatry warrants investigation. However, Williams and Balestrieri's demonstration (*Journal*, January 1989, **154**, 67–71) of a correlation between admission trends and increased psychiatric input at general practice level could be accounted for by other factors not examined in their study. These factors include community psychiatric nursing services, day hospital usage, and frequency of domiciliary visiting. The levels of these may reflect the style of services which are also more likely to include general-practice-based psychiatric clinics. It may be that the most important contribution of such clinics to the service is that they enable contact to be made with patients who would be reluctant to attend other forms of psychiatric clinics.

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The mind-body problem

SIR: Simpson (*Journal*, December 1988, **153**, 846–847) and I (*Journal*, July 1988, **153**, 123–125) agree that there is a place for philosophy in the medical curriculum, but he finds my dualism too uncompromising and suggests that a dialectical materialism as pioneered by Marx and Engels is a framework sufficiently complex to allow for the 'scientific' study of mind.

Let me admit at once to being a *reluctant* dualist. I only wish a tidy monist solution (especially for the biological – psychological controversy in psychiatry) were in sight, not to say at hand. But the prospect seems remote.

I used the word 'dynamic' not to allude to the give-and-take of various forces described by dialectical materialists (usually in the field of economics) and by some psychologists (usually discussing the unconscious), but as a short-hand label to distinguish 'psychoanalytic' psychiatry from 'organic' psychiatry. The feature of the former that makes it an unsuitable topic for a materialist is not its dynamism, indeed, but its *mentalism*.

A six-year-old boy complains of a stomach-ache every weekday morning, and the doctor thinks he does not want to go to school. The case is referred to a psychiatrist who happens to be a dialectical materialist. He explains the stomach-ache as the brain's perception of muscle cramps, and these as a result of various conflicting neural and humoral stimuli. The stimuli originate in conflicting attitudes to school-going which have their counterparts in other brain-states.

But what does the dialectical materialist psychiatrist do with the aches, the desires, and the doctor's opinions themselves? They are not material entities. (We cannot CT scan them, and would be nonplussed if they turned up in a CSF sample). They are mental entities (if one is a dualist), or statistical probabilities of certain behaviours (this works modestly well for desires and opinions – less so for aches); or perhaps they are the 'software' or 'program' that charts the logical connections between the various brain-states involved (the 'hardware') (this is the modern solution called 'functionalism'). Or again, the aches and the brain-states may be two different aspects of a more basic thing we simply cannot understand called 'persons', as the wave theory of light and the corpuscular theory of light describe different aspects of a subtle physical phenomenon to which no one theory can do justice.

I cheerfully admit that each of these solutions is imperfect. But materialism has its shortcomings no less than any other theory.

I hope that this correspondence reinforces the point on which Dr Simpson and I agree: that even the simplest psychiatric formulations have philosophical underpinnings, and that these underpinnings are problematic. That is why we should occasionally unearth them and study them.

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Psychological-mindedness and the alexithymia construct

SIR: Coltart's description of psychological-mindedness (*Journal*, December 1988, **153**, 819–820) and the guidelines she provides for assessing this feature in the diagnostic interview should prove helpful to psychiatrists in detecting patients who are unlikely to benefit from analysis or analytical psychotherapy. We would like to point out that the absence of psychological-mindedness is now usually subsumed under the broader construct of 'alexithymia', which evolved from observations of the cognitive/affective style of patients who were unresponsive to insight psychotherapy (Taylor, 1984). The clinical assessment of psychological-mindedness can be supplemented by administering to patients a recently developed self-report measure of alexithymia – the Toronto Alexithymia Scale (TAS). Investigations have shown that this is a reliable and valid instrument (Taylor & Bagby, 1988).

Derived from clinical observational data, the alexithymia construct encompasses several of the characteristics discussed or alluded to by Coltart, including (a) difficulty identifying and describing affects, (b) an inability to use affects as signals of inner conflict or of responses to external situations, (c) restricted imaginative processes, as evidenced by a paucity of dreams and fantasies, and (d) an externally-oriented cognitive style. Lacking access to feelings and other inner experiences, alexithymic individuals tend to focus on and amplify the physiological component of emotional arousal. This is thought to explain their tendency to somatisation and their proneness to discharging tension through binge-eating, substance abuse, and other compulsive activities – behaviours that were first reported in this type of patient by Horney (1952).

While some psychiatrists associate psychological-mindedness with socioeconomic status, educational level, and intelligence, our research with the TAS has shown no relationship between alexithymia and these variables in normal adults. Investigations with the TAS have also provided considerable empirical support for the validity of both the scale and the alexithymia construct (Taylor & Bagby, 1988). For example, factor analysis studies of the TAS have demonstrated a stable and replicable 4-factor structure theoretically congruent with the alexithymia construct. In addition, the TAS has been shown to correlate in predicted directions with measures of other constructs, including the psychological-mindedness subscale of the California Personality Inventory, the Need for Cognition Scale, the Anger Expression Scale, and the Short Imaginal Processes Inventory. Consistent with Coltart's view that the prospect of successful treatment is influenced by the level of psychological-mindedness, the TAS was also found to correlate strongly and negatively with Barron's Ego Strength Scale, a test that was designed to predict successful response to psychotherapy.

Given their unsuitability for analytical psychotherapies, patients who are not psychologically-minded have been largely neglected by psychoanalysts. The formulation and validation of the alexithymia construct, however, has focused attention on this difficult group of patients and prompted some analysis to devise modified psychotherapeutic techniques for treating them (Krystal, 1988, Taylor, 1987).

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Illicit drug use in strength athletes

SIR: We are currently conducting a psychological investigation with strength athletes, some of whom illicitly self-administer performance-enhancing drugs. The use of these drugs, mainly anabolic steroids, is widely recognised (Pope & Katz, 1988). We have been surprised by the willingness of these amateur athletes to try new drugs offered by friends and fellow competitors, despite little knowledge concerning their effects. In a recent example, a young male bodybuilder (aged 22) took 1000 mg L-dopa per day for three days in the belief that it would make his veins more prominent, thus enhancing muscular definition (an important attribute in bodybuilding competitions). He suffered flashes and pulses of pain in his head and experienced auditory hallucinations. This confirms the hallucinogenic properties of L-dopa reported elsewhere (Bradley & Hirsch, 1986). Following drug withdrawal these symptoms disappeared, and he has now returned to taking anabolic steroids. Steroids, however, may also cause negative side-effects: feelings of anger and hostility (Goldman, 1984), physical acts of violence (Pope & Katz, 1989), manic or psychotic episodes (Pope & Katz, 1988), and depression on drug withdrawal (Pope & Katz, 1988). Similar occurrences have been noted in our study, although causation could not be established.

The honesty of this athlete in admitting to drug use contrasts with the more frequently encountered reluctance. Amateur or professional athletes may therefore present for medical consultation with symptoms relating to illicit drug use. It is suggested that this should be suspected and objectively monitored before alternative diagnoses are offered.

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Corrigendum

Journal, December 1988, **153**, 796 (N. Kreitman & P. Casey). Table VI was omitted: it is given here.

TABLE VI

Rates per 100 000 by social class and category (average of three cohorts, males only)

Social class	*First-evers*	*Minor repeaters*	*Major repeaters*
I & II	58.4	40.1	10.2
III	112.2	74.3	17.6
IV	208.8	154.6	78.5
V	450.4	443.0	277.8

A HUNDRED YEARS AGO

The education of idiots and imbeciles

It is now a matter of common intelligence that a large proportion of the inmates of Asylums for Idiots and Imbeciles are capable of instruction. Not only is this true of ordinary school tasks, of course in a limited degree, but it applies also to the case of trade handicrafts and rational amusements. Shoe-making, tailoring, straw-hat making, weaving, and other occupations have thus been taught and learnt, and the success attained is on the whole encouraging. With material apparently so unpromising to deal with, the temptation to do nothing by way of education must be considerable, the more so since it has proved in the case of a substantial minority of the pupils practically hopeless. The marked success attained in other instances is a monument to the perseverance of those who achieved it. It is also an example of really useful work done by conserving, so to speak, the scraps of the national intellect, and it affords a strong argument in favour of the support of those institutions in which this work is carried on.

Reference

The Lancet, 19 January 1989, 136.

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British Journal of Psychiatry (1989), **154**, 734–737

Books Reconsidered

A Critical Dictionary of Psychoanalysis: Charles Rycroft*

The renown of this book rests on the single word 'critical'. Had it simply been called *A Dictionary of Psychoanalysis*, it might never have featured in this series of outstanding books of their time. The introduction of the word 'critical' implied that the book was going to tell the reader what was wrong with psychoanalysis; and this is what many non-analysts would like to know. Four years after its first appearance it was published by Penguin, who were no doubt aware that the critical element was its main selling point. They emphasised this by displaying on the front cover an absurd and vulgar sketch combining the face of Freud with a large, protuberant breast.

On the first page of the book Rycroft acknowledged that it grew out of a notebook in which he had recorded his puzzlement and doubts about certain aspects of Freudian theory. I would like to suggest that reaching the point of publicly proclaiming one's disagreement with Freud represents a stage in the development of the psychoanalyst which is the equivalent of what Bowen, the family therapist, has called the differentiation of self from the family of origin. Many prominent theorists such as Jung, Adler, Reich, Klein, Suttie, Balint, Berne, Bowlby, Perls, and Laing reached and passed through such a stage. In fact, the Freudian system lends itself to such a process. The aspiring analyst must seek admission to the system and then submit himself to a rigorous and regressive training ritual, during which his analyst, I would suggest, becomes for him what Kohut has called a self-object. Only when he emerges on the far side of this experience can he decide how much of what he has been exposed to he is going to absorb into his own identity and how much he is going to reject.

We know from Peter Fuller's excellent biographical introduction to Rycroft's more recent *Psychoanalysis and Beyond* (1985) that Rycroft did not take easily to the Freudian system. He is quoted as saying, "If I had known about the psychoanalytic movement and its quasi-sectarian quality, I would certainly not have applied". He did apply, submitted himself to the training, and emerged a qualified psychoanalyst, at the age of 33, in 1947. At this time the ideological battle between Anna Freud and Melanie Klein was at its most intense. Initially he veered toward the Kleinian viewpoint, but subsequently he tried to to maintain a middle ground. He largely conformed, became a training analyst, sat on numerous committees, and held various offices within the British Psycho-Analytical Society, but he became progressively more disenchanted with the way that polemics were conducted within the Society.

Shortly, however, he himself became caught up in disputes and controversies. In 1956 he caused a stir with the publication of his paper 'Symbolism and its relationship to the primary and secondary process'. In this, he challenged the official view that symbolisation was invariably unconscious, regressive, and defensive. This is a view which had been re-emphasised by Ernest Jones, Freud's leading British disciple, in 1916, in an authoritative paper called 'The theory of symbolism'. During the next 20 years, in what I would consider to be his attempts to extricate himself from Freudian orthodoxy, he published a number of papers which were critical of Freud. He came to realise, however, that his voice carried little weight in the Society's affairs and that the real power was in the hands of those whose values he did not approve. As Fuller expressed it, "... the weight of orthodoxy was such that any open confrontation with it inside the Society would have dragged him into precisely those rituals of polemic and pronouncement of anathemas that he was seeking to reject". He submitted his resignation, but he was persuaded to withdraw it. He was warned about how damaging it would be for the movement to have further splits. Eventually, in 1978, he let his membership lapse. Thereafter his two most important books were published, *The Innocence of Dreams* in 1979 and *Psychoanalysis and Beyond* in 1985.

The Critical Dictionary appeared, therefore, midway between the publication of his first critical paper and his final departure from the Society. In the first sentence of the book Rycroft appears to be struggling with his obvious ambivalence towards psychoanalysis. He explains that the book is not intended to be a dictionary of criticisms of psychoanalysis or to provide ammunition for those who may wish to demolish it. Instead, it is intended to help those who wish or need to inform themselves about it to do so intelligently and critically. Thus he intended to be constructively rather than destructively critical. In fact, he only allowed himself to be mildly critical and, for the most part, the book is a straightforward explanation of those psychoanalytic terms which had been in use up to the mid-sixties. The length of the explanations ranges from two lines to two pages, and in some of the longer explanations there are pointers to Rycroft's major disagreements with Freudian orthodoxy. To fully appreciate what those disagreements amount to the reader would need to refer to his longer texts.

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*London: Nelson (1968).

The dictionary proper is preceded by an 18 page introduction which raises a number of interesting points about psychoanalysis. The reader is reminded that most of the psychoanalytic literature was originally thought out and subsequently written in German and that, although most of the translations are excellent, it seems likely that some ideas are not easily transported from one language to another. The German word *Angst*, for example, is more heavily laden with overtones of anguish and fear than is the English word anxiety, and this may lead to the incorrect assumption that the normally adjusted person does not become anxious. It is suggested that the German tendency to precede abstract nouns by a definite article, to write "the consciousness" rather than consciousness, and presumably "the unconsciousness" rather than unconsciousness, has the effect of implying that such abstractions have a real existence and may be invoked as explanatory agents. It is further explained that, in English, there is one vocabulary (derived from Anglo-Saxon) for describing everyday ideas and experiences and another (derived from Latin and Greek) for thinking and writing about abstract concepts. We use the Anglo-Saxon word 'I' to refer to ourselves, and the Latin or Greek word 'ego' to refer to the more abstract conception of the self. The equivalent German words are 'ich' and "das Ich". This, it is argued, causes the English reader to dissociate the more impersonal structure of the ego, with its characteristics and functions, from what is really nothing other than the person himself. I feel that here Rycroft is blurring a distinction which really does exist. Jacobson, for example, has argued in the reverse direction: that Freud himself sometimes used the term 'ego' to refer to a psychic structure concerned with the ego functions and defences, and sometimes used it to refer to the self. The two concepts are, in fact, so distinct that there are now two separate psychoanalytic schools, the ego psychologists led by Anna Freud and Hartman and the self-psychologists led by Kohut and Kernberg. Ironically, in the main body of the dictionary Rycroft does draw a distinction between the ego and the self, and correctly draws attention to the preoccupation of the existential psychoanalysts with such a distinction. He makes no reference, however, to self-psychology or to any of the self-psychologists whose writings were not widely recognised in the mid-sixties.

From this point on, I will concern myself with various preoccupations of Rycroft's which are alluded to in the explanations provided in the dictionary but which are more fully examined in his longer texts. I will begin with his dissatisfaction with what he considers to be the implication of psychoanalysis, that man does not have a will of his own. He considers that it was Freud's belief that the human ego is a passive entity lacking energy or force of its own and only capable of action in so far as it is acted on by forces external to itself. These forces may be located either in the (unconscious) id or in the environment. This places man in the same category as the animals. Under the heading 'Will' he maintains that the concept of will forms no part of psychoanalytic theory, being incompatible with the assumption of psychic determinism and with the idea that mental illnesses are caused by unconscious processes to which the notion of will is obviously inapplicable. Under the heading 'Psychic determinism' he explains that such an assumption leaves no place in analytic theory for a self or agent initiating action or defence, or for the use of explanations other than causal ones. He maintains that most analysts believe that the claims of psychoanalysis to be a science are based on its use of causal-deterministic assumptions. He further claims that psychoanalysts need to view the neuroses as being illnesses like physical illnesses in which the patient is a victim of circumstances which impinge on his body without his own will being in any way implicated. There are clearly other reasons why psychoanalysis can lay claim to being a science, and it is not necessary for the patient to be viewed simply as the passive recipient of forces in the way that a physical object is.

Somewhat unconvincingly, I feel, he tries to proffer the influence of early experiences to justify his belief that the ego is not a passive entity. Under the heading 'Development' he states that psychoanalysts believe that adult behaviour can be interpreted as an elaboration or evolution of infantile behaviour and that complex 'higher' forms of behaviour can be interpreted as elaborations of simple, primitive behaviour patterns and drives. The developmental process as a whole can be considered to result from the evolution of innate developmental processes and the impact of experience on these processes. In the introduction he explains that, in the neuroses, the patient appears to be suffering the consequences of relationships in which he must have been, to some extent at least, a willing agent. It is not entirely clear to me why this leads him to conclude that the ego is, in fact, an active agent, capable of initiating behaviour, including those ultimately self-defeating forms of behaviour we know as the neuroses. It seems to me that one could interpret Rycroft's preoccupation with free will as a manifestation of his own internal conflict over the extent to which he should allow himself to be a passive recipient of Freudian dogma and the extent to which he should exert his own free will in standing up against the orthodox psychoanalytic position.

He goes on to argue that if the ego is an active agent, rather than a passive entity, it cannot be possible to maintain that everything that goes on between analyst and patient is "a scrambled repetition of the patient's childhood", with the analyst acting as a "completely detached, though benevolent observer". It is his belief that, although psychoanalysis was formulated as though it were based on the objective and detached scrutiny of 'material' presented to the detached and uninvolved analyst by the analysand, its insights really arise out of the relationship that develops "when two people are gathered together in a psychotherapeutic setting". He considers that the raw material or basic data of his science is the relationship he is having with his patients. Any reference he might have made early in his career to the "psychic apparatus" was, in his opinion, "making kow-towing movements towards classical theory". It has often been observed that Freud's tendency to present his theory in terms of structure and apparatus was a continuation of his medical and neurological patient-centred orientation. Rycroft's prediction that, one day, psychoanalytic theory will have to be reformulated as a communication theory is very much in line with Szasz's long-held belief that psychiatry is really a science of communication and Sullivan's interpersonal approach both to psychoanalysis and to psychiatry as a whole. (The quotations in this paragraph are from Fuller).

From the publication of his first critical paper in 1986, Rycroft continued to be preoccupied with the distinction between the primary and secondary processes, which he believed to be Freud's most important contribution to our understanding of mental functioning. There is, however, a fundamental difference between Freud's conception of these two processes and Rycroft's. Under 'Processes, primary and secondary' he explains that Freud believed primary process to be ontogenetically and phylogenetically earlier than secondary process, that it was that mode of thinking which was operative in the id, and that it was characteristic of unconscious mental activity. Secondary process, on the other hand, was that mode of thinking which was operative in the ego, and it was characteristic of conscious mental activity. Primary process was governed by the pleasure principle, whereas secondary process was governed by the reality principle. Rycroft maintains that Freud considered the two processes to be mutually antagonistic, that secondary process was superior because it developed later, and that primary process was primitive and maladaptive. Rycroft explains that psychoanalytic observation and theorising is involved in the paradoxical activity of using secondary process to observe, analyse, and conceptualise that form of mental activity (i.e. primary process) which scientific thinking has always been at pains to exclude. Rycroft believes that, in fact, the two processes complement each other and that they are equally adaptive and equally necessary for creativity. It is certainly the case that, in dreaming, primary process is most evident, but secondary process also occurs. Similarly, although the conscious thought of most adults is predominantly primary process, secondary process is also sometimes apparent.

Probably one of Rycroft's most important modifications of Freudian theory is his elevation of primary process to a status equal to that of secondary process. It seems highly probable that primary process does represent an earlier form of psychic functioning. It is a feature of the thinking and conceptualising of primitive people and of ancient mythology. Children exhibit a great deal of primary process before they are taken over by an educational system which emphasises the importance of logic and precise grammatical expression. It is, however, an essential component of creative thinking, regardless of whether this be of an aesthetic or a scientific kind. Under 'Creativity' Rycroft observes that psychoanalysis has always been tempted to demonstrate similarities between creative activity and neurotic processes. Freudian analysts, he claims, interpret the content of novels and paintings as an oedipal fantasy. Kleinian analysts have tried to prove that creative activity is either depressive or schizoid, that it either represents an attempt to make reparation for destructive fantasies or is in some way analogous to the delusional system-making of schizophrenics. He notes that since classical psychoanalysis designates imaginative activity as primitive, infantile, and a function of the id, writers such as Hartman and Kris have been driven to describe it in terms such as regression at the service of the ego. Creativity is individualistic and therefore, more than anything else, is difficult to include within a causal-determinist framework. At the end of his life Freud rejected the idea that psychoanalysis has anything to contribute to aesthetics. In contrast, Rycroft has constantly emphasised that imagination is a natural, normal activity of an agent or self. He has an acute awareness of the role played by the imagination at every level of mental functioning.

Not suprisingly, Rycroft has also challenged the Freudian attitude to dreams. His book *The Innocence of Dreams* (1979) represents an alternative to Freud's classic *The Interpretation of Dreams* (1900). Under the heading 'Dreams' he explains that Freud's interest in dreams derived from the fact that they are normal processes, with which everyone is familiar, but which none the less exemplify the processes at work in the formation of neurotic symptoms. For Rycroft, dreams are not necessarily disguised expressions of repressed wishes, the royal road to the unconscious, nor analogies for psychopathological symptoms. He maintains that dreams are merely the form which the imagination takes during sleep and that there is no reason to suppose that symbolism is essentially a device by which dreamers deceive and obfuscate themselves, even though on occasion it may be used in this way. Freud considered dreaming to be essentially a visual rather than a verbal process, and that dream interpretation involves expanding the condensed, non-discursive, mainly visual imagery of the dream into the discursive symbolism of language, i.e. of converting primary process into secondary process. Since Rycroft considers the two processes to be complementary he would not be in favour of translating one into the other.

What appears to be behind most of Rycroft's criticism of Freud is his dissatisfaction with the concept of the unconscious and with the fact that the individual is helplessly and passively controlled and directed by instinctual forces and reactions which originate within the unconscious. Under the heading 'Unconscious' he observed that patients with a speculative turn of mind may, if they have an unwary analyst, entertain an indefinite number of hypotheses about their unconscious motives without having any idea how to decide which of them are true. While he seems prepared to acknowledge that there are unconscious mental processes and also unconscious thoughts, he seems unable to accept the idea of entity called the unconscious which has a kind of autonomy of its own.

Where then does all this leave us? Rycroft is of interest because he is a psychoanalyst who rebelled against Freudian orthodoxy. Most psychoanalysts who rebel are able, through their rebellion, to make important contributions in their own right. Some rebel more strongly than others, and the originality of their contribution is a reflection of the intensity of their rebellion. Fritz Perls, who once wrote, "It took us a long time to debunk the whole Freudian crap . . ." rebelled a lot more strongly than Rycroft has and, in so doing, created the excitingly innovative Gestalt therapy. Rycroft's rebellion has been a relatively modest affair, but is no less valuable for that. Although no longer a member of the British Psycho-Analytical Society, he remains true to the psychoanalytic tradition.

Whatever critics may say of the efficacy of psychoanalysis as a form of treatment, there is no doubt that psychoanalysis has created a means of accomodating the subjective, the emotional and the irrational and provided a conceptual framework within which to generate theories about psychological development and human motivation. Along with all of this it has created a language, and all languages require a dictionary. Now that a dictionary exists it is capable of being expanded and updated and, now that Rycroft's has come of age, it is to be hoped that somebody, if not Rycroft himself, will come forward and take on this onerous but necessary task. Finally, it would be sad if all that Rycroft were remembered for was his dictionary. In the dictionary there are only pointers to his theoretical position. Hopefully this brief review will stimulate the reader to seek out his more substantial contributions.

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Book Reviews

Editor: Sidney Crown

Hypnosis: Current Clinical, Experimental and Forensic Practices. Edited by MICHAEL HEAP. London: Croom Helm. 1988. 448 pp. £30.00.

The editor is a psychologist and Honorary Secretary of the British Society for Experimental and Clinical Hypnosis. He remarks that until the founding of this society in 1978, training in hypnosis in Britain was only available through the Society for Medical and Dental Hypnosis, which restricted its teaching to those professions. Nevertheless, I recall receiving my own first instruction in hypnosis from a psychologist, the late Professor O. L. Zangwill, when I was a medical student and student of psychology as well. The present volume was organised as an attempt to produce a serious and informed cross-section of work on hypnosis at the present time in Britain and Ireland. As such, it provides an extensive and representative statement of current opinion, practice, and research.

After introductory chapters on the nature of hypnosis and its history, there are sections on experimental and theoretical issues, and on applications to relaxation and anxiety management, to psychosomatic medicine and dentistry, to psychological therapies, to children, to occupational psychology and sport, and to the forensic field. Legal and professional issues are also considered. At the beginning, Heap acknowledges that "in the laboratory it has proved surprisingly difficult to distinguish the performances of subjects who have undergone a hypnotic induction procedure from those merely instructed to behave as though they had". Wagstaff, a little later on, observes that there is a continuing controversy between those who think that hypnosis does involve a special altered state of consciousness and those who disagree. He notes that state theorists rely on Hilgard's 'neo-dissociation theory'. Although it is a little difficult to know if Wagstaff is sitting on or off the fence, this is an objective and informative chapter. Subsequent contributions on physiological and neuropsychological effects do not provide enough evidence to support the possibility that hypnosis causes more physiological change than other forms of suggestion.

Two chapters by J. B. Wilkinson may be among the most useful to the psychiatrist working in psychosomatic medicine. He describes the techniques for the control of hyperventilation and anxiety, and also some of the role of hypnosis in the treatment of asthma. There is reason to be increasingly conservative about the role of psychological factors in the production of such illnesses as asthma and irritable bowel syndrome (which is also considered). Chapters on these topics do show that hypnosis may be used in clinical practice, if only as an alternative to other methods of suggestion. Some of the material takes into account the effects in control groups, but there is not enough description of control procedures in most instances here. One would have to turn to the original papers to determine whether or not they were satisfactory.

Applications to purely psychological states and their treatment are reviewed, and this section includes a sympathetic, albeit critical, appraisal of the late Milton Erickson by Peter A. McCue. On the whole, this section on forensic issues contains well-argued articles. There is a sensitive and reasonable statement by Haward with a good deal of detail about the ways in which hypnosis can be used in the legal context. He is strongly supported by Mottahedin. A more sceptical approach is taken by Chief Inspector Michael Frost from the Police Staff College, and by others such as Mingay and Wagstaff who have looked at alternative systematic evidence. This is a good section for anyone wishing to be informed on this aspect of hypnosis. Finally, there is an interesting pair of chapters which deal with restrictions on the use of hypnosis and the problems of stage hypnotism, and provide a helpful review of events of recent decades which govern the attitudes of the public, professionals, and legislators to hypnosis in Britain.

The general tone of the contributions is moderate and reasonable. There are some good surveys, but still much that is anecdotal or provides a framework without proof. The volume as a whole did not leave me thinking that hypnosis would be able to add more to current knowledge or treatment than the alternative techniques such as exploratory and supportive psychotherapy, relaxation, and cognitive therapy. Overall, however, it is sensible and practical and will provide an excellent source for orientation. The printing appears to be photoreproduction from one typewriter. It is acceptable, and the volume is nicely bound.

H. MERSKEY, *Professor of Psychiatry, University of Western Ontario, Research Department, London Psychiatric Hospital, London, Canada*

Suffering: Psychological and Social Aspects in Loss, Grief and Care. Edited by AUSTIN H. KUTSCHER. New York: The Foundation of Thanatology. 1986. 196 pp. $32.95.

This is an interesting, rather philosophical book, as its title would suggest, rather than one which is intrinsically clinical and practical. It seems to aim at stimulating physicians to think about the practice of medicine, the nature of the doctor–patient encounter, and the fact that, as one contributor points out, "We are all patients – it is just that some of us become physicians as well". He suggests that for the doctor to have suffered a serious illness is one of the best ways to improve the therapeutic relationship. While personal experience does undoubtedly improve many physicians' insight, most doctors have little experience of serious illness, and yet many of them do develop helpful and insightful empathy into the patient's condition.

Most of the topics dealt with are of relevance to general medicine, and many to terminal illness, dying, and loss of the future. They could be of interest also to psychiatrists, especially the portion dealing with suffering in chronic mental illness. Those who practise in liaison–consultation and those who support or consult in hospices or other terminal care teams will find this book of particular interest. It is well referenced and researched, and would be a useful adjunct for a general medical or postgraduate library. At the price it may be rather too specialist for most general hospital or psychiatric hospital libraries, but it would certainly be of use to those preparing papers on aspects relating to terminal illness or working in a hospice and other related settings, depending on the budget available.

K. BLUGLASS, *Consultant Psychiatrist, Senior Clinical Lecturer, Department of Psychiatry, University of Birmingham*

Psychopharmacology: Current Trends. Edited by DANIEL E. CASEY and A. VIBEKE CHRISTENSEN. Berlin: Springer-Verlag. 1988. 212 pp. DM128.

This book is based on a symposium held in Denmark in 1987 which aimed to assess the present state of knowledge in psychopharmacology. The contributors are international and eminent, with a preponderance of Scandinavians. The largest section is on schizophrenia, with smaller ones on affective disorders, anxiety, and dementia. Contributions vary in nature from well-referenced and informative reviews down to subjective overviews, and topics range from basic pharmacology to clinical management.

The section on schizophrenia has useful short reviews of acute and long-term neuroleptic treatment and side-effects, including tardive dyskinesia. It is striking that our knowledge of even basic issues such as optimum dosage and time course of response is incomplete. Other more pharmacological reviews focus on receptor effects and pharmacokinetics of neuroleptics, and future research strategies for finding new antipsychotic drugs.

More disappointing is the section on affective disorders. Important current areas of interest such as the new antidepressants, the use of anticonvulsants, and receptor changes during chronic antidepressant treatment are mentioned only in passing. There are adequate, although limited, reviews of the management of treatment-resistant depression, the long-term treatment of unipolar depression, and the new monoamine oxidase inhibitors, but other contributions are less interesting.

The long-term treatment of anxiety is discussed with particular reference to problems with benzodiazepines, but lack of space sadly precludes discussion of other advances in the pharmacotherapy of anxiety, such as the use of antidepressants. New directions in the search for a drug treatment of dementia are discussed in two chapters.

The psychopharmacologist would be interested in leafing through this book, but would not be significantly disadvantaged by missing it. The general psychiatrist wanting a broad overview of advances in psychopharmacology could more profitably look elsewhere. Although there are several exceptional chapters, the book overall adds little to existing literature and is probably not a worthwhile purchase for the general psychiatric library.

MALCOLM PEET, *Senior Lecturer in Psychiatry, University of Sheffield*

Family Therapy in the Community. By DUNCAN MACPHAIL. Oxford: Heinemann. 1988. 192 pp. £9.95.

I welcomed a basic family therapy book written by a Community Psychiatric Nurse (CPN) for CPNs. We have had CPNs in our clinic for some years, and they read this book too before I did the review. The author starts by saying that he is writing a practical manual rather than a theoretical text. However, there was a sense of rushing through the theory at the beginning, which does not develop a sound theoretical base on which to develop practice, and might be more confusing for a beginner than a slower paced look at the basic theory.

There are some well set-out exercises at the end of each chapter to consolidate what has been read, and a reading list on the chapter. Much of the rest of the book is based on clinical examples, which sometimes seemed an idiosyncratically chosen mixture, and it is here that the difference between nurses based in clinics as part of teams and nurses based in clinics as part of teams and nurses attached to general practitioners' surgeries begin to become more apparent.

The short discussion on confidentiality was not particularly helpful and did not take up the complicated areas of sharing information between different agencies. This needed to be described systemically, as would have been appropriate in a book about family systems.

This is a general flaw in the book. Although at the beginning MacPhail talks about the way that thinking systemically alters views of pathology and the meaning of behaviour, by the end he was writing short sections on specific pathologies.

This is not a basic book that could stand on its own. However, CPNs in our clinic felt it was important that books by nurses were being produced, and it certainly spurred them on to think more optimistically about writing themselves. As CPNs have tended to be the latest group to join multidisciplinary teams and there is a continual debate about their role, it would be useful to have this book alongside others in a clinical or team library.

RACHEL LEHEUP, *Consultant Child Psychiatrist, Child and Family Therapy Service, Nottingham*

Learning Psychiatry through MCQ. A Comprehensive List. Edited by TOM SENSKY. Chichester: John Wiley. 1988. 259 pp. £9.95.

This book is unusual among the ever-increasing number of multiple choice question (MCQ) books on psychiatry in that it is written primarily for medical undergraduates. The authors also rather ambitiously intend to provide a comprehensive account of general psychiatry, but it is unclear in the preface whether they aim to replace or to supplement traditional medical student textbooks.

There are 136 questions arranged under 13 subject headings, and 10 case histories. As an admittedly biased psychogeriatrician, I feel old age psychiatry merits a separate section rather than being subsumed under organic psychiatry, with little recognition of functional mental illness in the elderly.

While generally the questions and answers are uncontroversial and contain useful basic information suitable for students, there are some surprising answers which contradict widely held views. The prevalence of enuresis among British ten-year-olds (question 101) is given as 10%, when the accepted figure is 5%. Similarly, the prevalence of dementia in those over 65 is stated as being 10–20% (question 22), when the usual figure given is 5–10%. The safe upper limits for alcohol consumption (question 73) are now out of date, having been revised downwards. Also, I doubt if "all social classes are represented equally among (opiate) addicts in Britain", and think it more likely that social classes 4 and 5 predominate.

A novel and interesting idea is the inclusion of the average scores of Charing Cross students for each question, together with a measure of its ability to discriminate between candidates. This is obtained by correlating the scores for each question with candidates' overall scores. I suspect that the discriminatory power of several questions could have been improved by removing the terms 'never' and 'always', which are giveaways to most students. The book would also be enhanced by the provision of an introduction giving advice on how best to tackle MCQs, together with information on the meanings of commonly-used terms such as 'typical' and 'characteristic'.

Overall this book will not replace a conventional psychiatric undergraduate textbook, although it would be a useful and stimulating revision aid for medical students. At £9.95 I think it is likely to be a group rather than an individual purchase.

ELAINE ARNOLD, *Consultant Psychiatrist, Central Middlesex Hospital, London*

The Milan Approach to Family Therapy. By GUIDO L. BURBATTI and LAURA FORMENTI. Translated by ELENA COSMO. New Jersey: Jason Aronson. 1988. 221 pp.

The Milan school of systemic family therapy is an internationally established voice within the movement inspired by the work of Gregory Bateson and his colleagues in Palo Alto. It applies insights and methodology derived from cybernetics to the analysis and treatment of problematic social behaviour. The authors of this book work in Milan, and are well qualified to describe the Milan approach to family therapy, one having been trained by members of the original Milan team and the other having co-operative contact with the Gregory Bateson Study Center.

The book begins with a clear exposition of the theoretical framework on which the Milan approach is based. The four following chapters describe different phases in treatment, including termination, when the therapy is evaluated. Each phase is illustrated by verbatim transcripts selected from the material provided by one family. On the whole, this method of presentation works, and the authors have done well in presenting so succinctly their use of concepts worked out in Milan and Palo Alto and embodied in the Batesonian/Milan paradigm as it is understood today. However, this systemic way of thinking about dynamic systems, let alone the language that has developed to express these ideas, is not always easy to grasp. Newcomers to this approach may still need to look up quoted references to the original description of concepts now encapsulated in words such as 'neutrality', 'circularity', 'positive connotation', 'paradox', and 'counterparadox'.

This book claims to be the first systematic attempt to describe and illustrate the theory and practice particular to the Milan school. However, the translation has joined two other recently published books whose authors include founder members of the school. Nevertheless, this volume demonstrates the breadth of the Milan approach to family therapy, and can be recommended.

DOROTHY HEARD, *Honorary Consultant Psychotherapist, St James's University Hospital, Leeds*

Relationships Within Families: Mutual Influences. Edited by ROBERT A. HINDE and JOAN STEVENSON-HINDE. Oxford: Clarendon Press. 1988. 406 pp. £42.50(hb), £22.00 (pb).

The bland title of this book does not even hint at the massive body of thinking and research it contains. The importance of the book, however, is not the volume of its findings, but the crucial nature of the task undertaken: to study the effects of relationships on relationships from a broad range of theoretical vantage points. The 22 contributors are all eminent in their respective fields. The book is based on a small invited conference convened by Hinde and Stevenson-Hinde in January 1987. Although all the participants were development psychologists, they represented a broad spectrum of thinking and research, from Patricia Minuchin (whose introductory chapter 'A systems perspective on development' gives an excellent summary of systems theory as applied to the family, and of related research and its limitations) to Michael Rutter (whose chapter on 'Some psychopathological considerations' provides an elegant review of the research into the effects of early unsatisfactory experiences on later relationships, including the most optimistic finding that 'a supportive marital relationship' could prevent a parent from repeating her own deprived childhood relationships with her children).

The importance of this work is not just academic. It begins to tackle some of the intrinsic problems of research into human emotional and cognitive development, and therefore has implications for many current theories in Psychiatry. These are commonly based on a mixture of conviction and clinical experience (in which case the latter allows observations which are almost entirely organised by the parameters of the convictions or 'philosophies'), and if tested by research this is usually based on observations of individual behaviour or on retrospective reports of individual experience. Hinde points out that interpreting such findings is difficult, because (a) influences between relationships are often mutual and circular; and (b) the effects implied by correlational methods are not necessarily the ones that really matter in terms of psychologically important processes.

The book begins to tackle these problems. In the discussion sections of the 18 chapters the authors acknowledge and are influenced by each other. There are five sections: 'Coherence within families', 'Marital and parent–child relationships', 'Parent first-born second-born relationships', 'Coherence across generations', and 'Families in distress'.

Not surprisingly, the main differences between the authors – what is defined as a valid field of study, and what are defined as valid methods of study – were at the heart of the conference. Minuchin reviews three child development studies in detail, but notes that, "Our information is incomplete or distorted if we do not study the patterns of the family as a whole" (and include fathers and siblings in particular). Sroufe to some extent tackles this problem through a study of patterning of relationships across different contexts, although fathers remained shadowy figures. Radke-Yarrow provides a relationship approach to understanding child development, but principally through dyadic relationships and as so often without the father being a member of any of the principle dyads studied. Stevenson-Hinde, while describing a study based on individual characteristics, also suggests a means whereby these characteristics may mediate the effect of one relationship on another. Easterbrooks addressed the mediating role a child's 'characteristics' may have on the parents' marriage, but only from a negative point of view, and the possible protective impact of a child's behaviour receives scant attention throughout the book. The best meeting ground is provided by Kreppner, who looks at the whole set of available relationships in families of four after the birth of the second child. Hinde's and Dunns' work are perhaps best known to British readers, and other chapters include applications of attachment theory and the impact of divorce. In an excellent epilogue Hinde attempts to both distinguish and integrate the different points of view represented. This task is not entirely possible, but this book makes a very important start on it.

All trainees in psychiatry, psychology and social work should become familiar with this book, and it would be wise if their trainers knew of it too.

ALAN COOKLIN, *Consultant in Family Psychiatry, Marlborough Family Service, Bloomsbury Health Authority, London*

Behavioural Psychotherapy in Primary Care: A Practice Manual. By T. CARNWATH and D. MILLER. London: Academic Press. 1986. 403 pp. £42.00.

The authors intend this useful book to be used as a manual by those wishing to practice behavioural psychotherapy in primary care settings. They describe techniques suitable for treating the majority of patients with psychological problems in such settings, and they aim to instruct not only general practitioners and psychiatrists but also paramedical mental health specialists, as well as nurses, health visitors, and counsellors.

The text is generally well written and contains many helpful illustrations and references. There are two main sections: principles and practices. 'Principles' contains chapters on behavioural analysis, problem solving, working with families, skills training, relaxation, exposure, stimulus and reinforcement control, paradoxical prescriptions, and cognitive therapies. 'Practices' deals with depression, phobias and obsessive disorders, anxiety, sexual dysfunction, behavioural medicine, illness behaviour and treatment adherence, obesity, alcohol abuse, smoking, and insomnia.

GREG WILKINSON, *General Practice Research Unit, Institute of Psychiatry, London*

Schizophrenia: The Major Issues. Edited by PAUL BEBBINGTON and PETER McGUFFIN. London: Heinemann. 1988. 262 pp. £25.00.

On her deathbed Gertrude Stein's penultimate words were reputed to be, "What is the answer?" As no-one spoke, she added, "In that case, what is the question?". I was reminded of her words when reviewing this book (prepared in parallel with a conference on new initiatives in schizophrenia research, held in September 1987). Although vastly more is known now than 40 years ago, it is still almost impossible to know which is the best question to ask. In a section on terminology Mackay made this very point:

> "Genetic, morphological, psychological, electrophysiological, and neurochemical evidence now surely makes it appropriate to include schizophrenia within the group of organic psychoses. Many psychiatrists still find this notion dangerously premature, and while the point may well be trivial, at least it serves to draw attention to the most obvious gap so far in the schizophrenia story. We do not have the vaguest notion of the nature of the brain dysfunction(s) which produces delusions and hallucinations, and only vague notions of the anatomical loci for these dysfunctions."

Some of the necessary questions are posd by Lantos, who reviews neuropathology and makes the (not surprising) point that:

> "A rather mixed and somewhat contradictory picture emerges. Clearly, there is no consensus on the constitution of the structural basis of this disease. Are the abnormalities diffuse or localised? Do they affect the cortical ribbon or the deep grey matter? What part of the cortex and which deep grey nuclei are preferentially involved? Are the nerve cells or glial cells the target of the disease process? Are the structural changes cellular at all or, more subtly, subcellular? After so many years, these questions still remain largely unanswered."

There are some facts on which we can agree. Deakin points out that any theory of the aetiology of schizophrenia has to accommodate the following facts:

1. There is a major genetic contribution to causation.
2. Neuroleptic drugs are effective in treating the symptoms.
3. Cerebral atrophy is associated with schizophrenia.
4. There is a small excess of winter births.
5. Onset occurs in the late teens and twenties.
6. Schizophrenic psychoses in temporal lobe epileptics are more likely to occur when the focus is on the left hand side."

The editors confirm the importance of definition. Epidemiology has contributed much to our knowledge, although it may contribute less in the future:

> "To the outsider, discussions among psychopathologists about how best to define, identify, and classify the phenomena of schizophrenia, and about how best to plot out the boundaries of the syndrome or to divide subgroups, must sound arcane and even a little like theological debate. The exact configuration of symptoms that are required to make a diagnosis is a less obscure and other-worldly issue than how many angels can dance on a pinhead, but the arguments sometimes have a similar flavour of knowledge through faith. Yet informed debate and continued research on how schizophrenia should be defined are vital. On them depends every statement about incidence, prognosis, response to treatment and the nature of neuropathological or biochemical changes. The introduction of operational criteria must, as we have already stated, be regarded as advantageous. However, there is a multiplicity of competing criteria, and even if one particular system gains ascendency for research purposes, the partially arbitrary nature of operational definitions will prevent it being a panacea for diagnostic difficulty.

Reviewing the effects that social influences have on the disease it can be seen that there has been some, although limited, progress:

> "Pragmatic rather than theoretical studies suggest that it is possible to identify at least four types of persistently 'toxic environment': the cognitivity confusing; the emotionally intrusive; the overly demanding; and the threatening or demoralising physical environments. (Of course the emotionally intrusive environment created by living with a high EE relative might be stressful because it was cognitively confusing)."

The possibility of amelioration of symptoms continues to improve. Stahl and Wets conclude that:

> "The clinical pharmacology of schizophrenia today comprises the use of typical neuroleptic drugs. These drugs produce extrapyramidal side-effects at the doses required to control psychosis. Dawning on the horizon is a new era of so-called atypical neuroleptic drugs. These drugs, now in early clinical trials, may reduce psychotic symptoms at doses which do not produce extrapyramidal side-effects. In the more distant future, several new treatments based upon novel pharmacological mechanisms are being developed: CCK antagonists and agonists, neurotensin agonists and antagonists, sigma opiate antagonists, and 5HT3 receptor antagonists."

Forty years ago when I was a medical student and first encountered a patient with schizophrenia, the illness was the same, but views about its nature differed. Henderson & Gillespie noted then that the cause of the condition was obscure and that they could "merely mention some of the more authoritative views and point out the lines on which they believed further progress might be made". That heredity plays a part would be the only statement with which we agree today. They noted that Kraepelin believed that "the mental-disease process resulted from an auto-intoxication following a disorder of metabolism, and that this auto-intoxication was produced by a disordered secretion of the sex glands". Lewis had found that "schizophrenics suffered from a state of aplasia of the circulatory system and an atrophy of the sex glands". Gibbs found that a considerable portion of schizophrenics had abnormal hair distribution (vertical pubic hair in females). Aldolph Meyer and his pupils included the view that schizophrenia was the outcome of progressive maladaptation of the individual to his environment. Kretschmer looked for dysplastic types, and Cotton eliminated focal sepsis (teeth and tonsils). The other treatments available were insulin, cardiazol, ECT, leucotomy, and continuous narcosis. The chief hope of success in treatment was believed "to lie in earlier diagnosis so that cases would not be brought to the psychiatrist only when the disorder was thoroughly established".

A little has been learned in the past 40 years, but infinitely more remains to be discovered. Nevertheless, at the meeting in September 1987 there was "a palpable excitement". For the first time there was a real possibility that we might at last learn something of the nature of this most elusive illness. In another 40 years most of what is in this book will have followed the dopaminergic hypothesis of Laing, Szazcs, and Cotton into the dustbin of history where failed and untestable hypotheses are ultimately stored. But the spirit of the conference, a determination to develop and refine testable aetiological theories, will doubtless have led to further real progress in our knowledge.

In the meantime I can strongly recommend this volume to anyone who wishes to update their knowledge of current research. It provides an excellent cross-sectional view of the state of play in 1988. There are 17 chapters and 25 contributors without much in the way of overlap, for which the editors should be congratulated. It should be compulsory reading for trainees until 1992.

THOMAS BEWLEY, *Senior Lecturer, Department of Addictive Behaviour, St George's Hospital Medical School, London*

An Introduction to Psychiatric Research. By RICHARD E. GORDON, CAROL J. HURSCH and KATHERINE K. GORDON. Cambridge: Cambridge University Press. 1988. 257 pp. £25.00.

This book starts with what is said to be a quotation from Lord Kelvin: "When you can measure what you are speaking about, and express it in numbers, you know something about it". The book comes to us from the Department of Psychiatry of the University of Florida, and is aimed at helping its readers to plan and execute small-scale individual research projects, as well as to evaluate critically papers in journals. The use of a wide range of statistical procedures is explained, and worked examples are given of most common tests, together with examples of computer printouts giving the same results. Useful early chapters deal with formulating an initial hypothesis and setting up a project, complete with useful bits of homely advice like having a notepad on one's bedside table in order to jot down brainwaves that occur to one during the night.

It all seems excellent, yet somehow it is *too* homely. The references at the end tell the story: they are mainly to the authors' own work, so that young readers are given little guidance about procedures and rating scales that originate outside Gainesville. The other problem concerns the statistics: if a reader is actually going to carry out a project, then they will need more information about any given procedure than is available here. However, the book is admirable in its way, and the alternative texts are beginning to show their age. The classification of research studies used as the framework for the book is a useful one, the authors are bursting with good advice, and it is the first book to come to terms with the fact that tomorrow's individual researcher must come to terms with a desk-top micro.

DAVID GOLDBERG, *Mental Illness Research Unit, University of Manchester*

Memory Disorders in Clinical Practice. By NARINDER KAPUR. London: Butterworths. 1988. 289 pp. £39.50.

'Clinical practice' in this case is that of a Regional Neurological Centre, so a general psychiatric reader of this book may feel he or she has been misled by its enticing title. The author, a neuropsychologist, takes inspiration from Lishman's classic work and approaches organic memory disorders in terms of specific cerebral diseases.

To a considerable extent, Kapur is successful. He adopts a clinical stance and avoids theorising as to mechanisms of different memory systems. Assessment of empirical data is thorough and even-handed, although at times a more didactic stance by the author would have been helpful. Discussions of available neuropsychological tests and test batteries, alcoholic Korsakoff's syndrome, and the mnestic results of brain surgery are particularly clear. The book is attractively produced, with numerous useful plates of CT scans, and the references (over 1000) are up to date.

When comparison with Lishman is made, it is clear that the prose style of the master has not been emulated. At times, the text begins to feel like a catalogue of abstracts. The discussion of memory disturbances in psychiatric disorders is brief and incomplete, which is disappointing as such deficits have much in common with more obviously 'organic' states. There are not too many misprints, but on page 131 there is probably a hidden cognitive test where an illustration of three scans is labelled in the wrong order.

The literature on memory disorders is now so large that it is probably a no-go area for many psychiatrists, particularly since the practical clinical yield from such work has so far been sparse. I did not find this an easy book to read straight through, as studying successive chapters tended to induce proactive interference! Perhaps this reflects the nature of the material as much as the manner in which it is presented, but I came to the conclusion that its main use will be as a reference text. The best guide to management of memory impairment in the more general psychiatric field remains that of Wilson & Moffat.

TOM DENING, *Senior Registrar in Psychiatry, St Crispin Hospital, Northampton*

The Regulation of Madness. The Origins of Incarceration in France. By ROBERT CASTEL. Translated by W. D. HALLS. Oxford: Basil Blackwell. 297 pp. £29.50.

Castel is one of a growing band of social historians, sociologists, philosophers, lawyers, and workers in kindred disciplines who, to no small extent, have taken over the historiography of psychiatry. This may be no bad thing if something is known about the provenance of these who choose to enter the field. In this instance there can be little uncertainty. Castel, in his introduction, makes abundantly clear his indebtedness to Michel Foucault, who, it will be remembered, together with Erving Goffman, Thomas Szasz, and R. D. Laing, spearheaded the antipsychiatry movement. Not only this, but he includes among his mentors Franco Basaglia who, in furtherance of his political objectives, was largely responsible for the introduction of legislation in Italy in 1978 which forbade the admission of further new patients to mental hospitals which were themselves to be run down and eventually closed. These Draconian measures have led to a new class of Italian vagrant – the *abondonati* – a host of homeless, mentally sick ex-patients who roam the streets and public places.

It will come as no surprise, therefore, to learn that Castel's approach to the institutional care of the insane in pre- and post-revolutionary France does not reveal French psychiatrists in a particularly favourable light. It is true, as he points out, that in 1790 the Constituent Assembly abolished the iniquitous *lettres de cachet* which under the *Ancien Régime* allowed an individual, usually of aristocratic family, to be incarcerated without further ado. It is also true that Pinel had the calm courage to liberate the inmates of French asylums from their chains. However, Castel insists that this legal and physical emancipation was illusory and was to be followed by a form of psychological control by psychiatrists, which was in its nature far more subtle, but far more complete.

Foucault lends his authority unambiguously to the views expressed by his protégé. In a note on the back of the book-jacket he writes: "From now on, psychiatry must live with its past. Robert Castel recounts this past with a strong and clear voice. It will, I'm afraid, make the reader groan: someone who is not a psychiatrist reconstructs a past which psychiatry would prefer to disown".

It is a matter of conventional wisdom that in any controversy it is advisable to know what the opposition is thinking. It is for this reason, and for this reason only, that I would suggest that colleagues read this book; except, perhaps, for those with a tendency to hypertension.

HENRY ROLLIN, *Emeritus Consultant, Horton Hospital, Epsom, Surrey*

Clinical Relaxation Strategies. By KENNETH L. LICHSTEIN. New York: John Wiley. 1988. 426 pp. £45.00.

This book is probably the most significant addition to the relaxation literature since Herbert Benson's *The Relaxation Response* was published in 1975. Primarily a work of synthesis, it provides an exhaustive and scholarly review of the research literature on relaxation strategies, barring the deliberate omission of hypnosis and biofeedback. Running to 300 pages of text, with over 1700 references and barely a table or diagram for light relief, it is a formidable project for author and reader alike!

Lichstein begins by reviewing the historical roots of relaxation, which he locates in the ancient Eastern meditation heritage, then leaps abruptly to 20th century developments. A consideration of basic theoretical and empirical research on three fundamental appoaches – meditation, progressive relaxation, and autogenic training – is followed somewhat belatedly by descriptive expositions of the main techniques and variants, as stand-alone or adjunctive interventions. Impatient clinicians will doubtless make a beeline for detailed outcome reviews in the final chapter, covering an 'A to Z' of clinical problems.

The book's organisation and indexing assist the reader coming to grips with this massive field. There are few obvious omissions, although I searched in vain for a definition of the central term 'relaxation'. Surprisingly, no mention is made of somatic techniques such as massage, either.

While Lichstein occasionally bemoans the trend towards a 'technology' of relaxation which regards brevity and symptomatic relief as its touchstones, his book is a paean to the accomplishments of this empiricist enterprise, which has elected to give the 'art', 'wisdom' and *raison d'être* of relaxation decidedly short shrift. Judging by his final remarks, Lichstein recognises that the impending scenario – of clients declining a newly-perfected brief relaxation technique because it can't be fitted into their schedules – is a deeper matter than a simple issue of 'subject compliance'.

Provided you are interested in the 'how' of relaxation more than the 'why', this impressive, dense, yet commendably readable book is an essential acquisition. It will be a godsend to researchers, and a stimulating and challenging sourcebook for clinicians, especially those who think that dispensing an audio cassette is the top and bottom of relaxation training. But, as a frustrated client once remarked about a pre-recorded tape: "The instructions were super, it was the voice that kept putting me off".

JULIAN FULLER, *Principal Clinical Psychologist, Butler Clinic, Langdon Hospital, Dawlish, Devon*

Modern Perspectives in Psychiatry, No. 10. Modern Perspectives in Clinical Psychiatry. Edited by JOHN G. HOWELLS. New York: Brunner/Mazel. 1988. 392 pp. $40.00.

This book consists of 17 articles each on a different topic and by a different author. The editor states that the volume is not intended as a textbook, that a complete coverage of clinical psychiatry is not attempted, and that the topics covered "select themselves". Certainly there seems to be no particular plan behind the choice of topics. Some are fashionable, e.g. 'AIDS and psychiatry' or 'From mental hospital to alternative community services'; others are standard topics which would be dealt with in most publications on clinical psychiatry, e.g. 'Epidemiology in psychiatry'; and 'Liaison psychiatry'; and yet others are more unusual, e.g. 'Systems theory in psychiatry' There is diversity too in the approaches taken by the authors. Some chapters provide well-organised and balanced, if fairly simple, accounts of the relevant topics, and others are at a more advanced level. Several are clearly written by enthusiasts whose intention has been to make a case for the subject of their choice rather than to present an even-handed account.

Most of the authors are from North America, and their reviews of the literature tend to have a transatlantic slant. Similarly, some of the accounts concern aspects of psychiatric practice in the United States which differ from the circumstances of practice of most psychiatrists in this country. For these reasons this book will not be particularly helpful for trainees preparing for the MRCPsych, but it is probably not for such an audience that it is intended. It is perhaps because I read this book over the holiday period that it reminded me of an old-fashioned Christmas anthology. It is a series of essays, some very careful, some a little trivial, others very informative and a few that are just different – for example, one which presented changing styles of psychiatric practice in relation to political, fiscal, and social changes in the United States.

I enjoyed this book and I would recommend it as a worthwhile purchase for any psychiatrist who is not thinking in terms of examinations but is looking for an informative and sometimes thought-provoking account of diverse issues related to current psychiatric practice.

EVE C. JOHNSTONE, *Member of the Scientific Staff of the Medical Research Council and Honorary Consultant Psychiatrist, Northwick Park Hospital and Clinical Research Centre, Harrow*

Handbook of Psychopharmacology Vol. 20. Psychopharmacology of the Ageing Nervous System. Edited by L. L. IVERSON, S. D. IVERSON and S. H. SNYDER. New York: Blenheim. 1988. 482 pp. $75.00.

Those familiar with this excellent series on psychopharmacology will greet volume 20 with mouth-watering anticipation. They should not, however, be misled by the title; the book is almost entirely about the psychopharmacology of Alzheimer's disease. It is none the worse for that, but readers interested in the nervous system of the normal elderly, those with functional psychoses, and those with multi-infarct dementia will find little of interest.

Furthermore, this book is intended as a sourcebook for those engaged in psychopharmacological research. It has excellent and authoritative reviews covering the subject in great detail, the first chapter for example containing nearly 400 references. Most psychiatrists will find that it contains more information than they can easily digest, and might prefer the review in the *British Medical Bulletin* on Alzheimer's disease, also edited by Iverson (and Ross), published in 1986.

Each of the 11 chapters is written by a different author, resulting in a certain amount of repetition, but with the advantage that each chapter can be read on its own. My last criticism is inevitable for a volume of this kind, in that it is already out of date. Thus there is only one mention of THA, the chapter on genetics makes no mention of molecular genetics, and there are only a tiny number of references after 1986.

The first chapter, by Mann, provides a masterly summary of the histological and biochemical features of Alzheimer's disease, including an interesting speculation about the sequence of events, suggesting that it may start with loss of the blood–brain barrier, followed by senile plaque formation, cell death from tangle formation, and retrograde degeneration to nucleus of Meynert. Hohmann *et al* focus on the cholinergic system in Alzheimer's disease, initially throwing doubt on the whole theory by quoting a study which showed that acetylcholinesterase was not a specific marker of cholinergic synapses; they conclude, however, that the cholinergic theory has most promise for therapy. Rossor writes a much briefer review of the biochemistry of many dementias, the section on Alzheimer's disease repeating those of earlier chapters. There follows a fascinating and more speculative chapter by Saper on neuroanatomy, in which he suggests that the damage in Alzheimer's disease starts in the multimodal areas of the enterorhinal cortex and spreads trans-synaptically to cause cell death in the nucleus of Meynert. Ruberg & Agid do a splendid job sorting out the difficult issues of dementia and parkinsonism, and there follows a chapter by Breitner on epidemiological genetics, including four recent studies from America. Hagan & Morris then contribute a chapter taking up one-fifth of the volume, on animal experiments relating to the cholinergic hypothesis. I find many of these experiments distasteful, and in any case they were largely unproductive. Many of them were invalidated by the ability of scopolamine to reduce arousal and stimulus sensitivity. Work on human beings suggests that scopolamine acts at the learning rather than the recall phase, but nearly all the animal experiments concentrated on the latter.

Dean & Bartus concentrate on primates, including, despite the title, humans. They also cover the area of therapeutic agents, which are reviewed in equal detail in subsequent chapters by Sahakian on cholinergic drugs, Mohs on vasodilators, and Poschel on nootropics. Although the last two chapters are well written and sensible reviews of their subjects, the choice is regrettable, since they concentrate on drugs which have little effect on dementia. I would have appreciated a more clinically based chapter on the treatment of multi-infarct dementia concentrating on treatments for hypertension, atheroma, and embolus formation. However, this might put the emphasis on clinical medicine, which is certainly not the object of the book.

There is no doubt that this book should be on the shelves of every medical school and every department of neuropharmacology and neurohistology. I have doubts as to whether it should be bought by every psychiatric hospital or for that matter every psychiatrist.

JOHN M. KELLETT, *Consultant Psychiatrist, St George's Hospital Medical School*

Perspectives in Psychiatry. Edited by PETER HALL and PETER D. STONIER. Chichester: John Wiley & Sons. 1988. 198 pp. £21.50.

This is a collection of 17 papers based on lectures given at Worcester between 1980 and 1987 and sponsored by drug firms. The authors are established (and mainly 'establishment') figures in psychiatry – all, significantly, men, and all white. The book is edited by two men, one a consultant at Worcester and the other a medical director of a drug firm.

The topics addressed in the book are varied, ranging from community psychiatry to pain, and from brain damage to puerperal disorders. The chapters are all written in a 'narrative' style. Each addresses a single topic, in most cases rather too broad in scope for the author to even attempt at being comprehensive. On the whole, the topics are dealt with in a traditional – almost old-fashioned – way. For example, the paper on schizophrenia may easily have come from a textbook written in the 1960s, and the paper on the treatment of depression is exclusively about the use of drugs and ECT. Three papers can be picked out as offering something in the way of new ideas and critical comments on the topics they address. Firstly, Birley's essay on community psychiatry is a useful discussion of the current scene from a traditional point of view. Secondly, Eames gives a good insight into the practicalities of dealing with patients with difficult behaviour. Finally, Bergman's rather discursive essay states bluntly the problems involved in carrying out 'preventive psychiatry' among the elderly.

This book is a collection of essays which are readable and fairly light reading. As a book, it does not make a substantive contribution to knowledge, but may be recommended as an adjunct to introductory lectures on psychiatry for, say, medical students or other professionals.

SUMAN J. M. FERNANDO, *Consultant Psychiatrist, Department of Psychiatry, Chase Farm Hospital, Enfield, Middlesex*

Computer Models of the Mind: Computational Approaches in Theoretical Psychology. By MARGARET BODEN. Cambridge: Cambridge University Press. 1988. 289 pp. £10.95 (pb), £30.00 (hb).

This is not just another artificial intelligence textbook; it is a journey through the uses of computational methods in simulating mental processes. It complements very well Boden's previous well-known book, *Artificial Intelligence and Natural Man*.

There are chapters on vision, natural language processing, reasoning, and learning. The book concludes with a discussion of the aims of 'computational psychology' and of the advantages and disadvantages of this approach to the development of theories. Boden is an acknowledged expert in this field, and writes with authority and style.

This is one of the first in the new breed of introductory book specifically addressing the issue of modelling cognitive processes as opposed to simple (!) writing programs which perform "intelligently". There is a great deal of fascinating research in this area which has not previously been covered in such books, and it is encouraging to see that this book does a good job of including such material. There are the old chestnuts such as Marr's theory of vision, which are probably dealt with at too great a length, but new approaches (including the 'connectionist' approach which is causing much excitement) are well represented. Attempts are made where possible to evaluate some of the models against hard evidence, and the tone of the book is appropriately cautious about the success or otherwise of current efforts.

This book will certainly be used in psychology undergraduate and postgraduate courses. I would like to think that it would be of interest to clinical psychologists and psychiatrists also, despite the concentration on normal cognitive functioning as opposed to disordered functioning and emotional and motivational models.

ROBERT WEST, *Lecturer, Psychology Department, Royal Holloway and Bedford New College, London University*

A Fresh Look at Psychoanalysis: The View from Self Psychology. By ARNOLD GOLDBERG. Hemel Hempstead: International Book Distributors. 1988. 275 pp. £22.95.

Goldberg enters the debate between psychoanalytical self-psychology and the classical theory as a supporter of Kohut, but one determined to avoid polarisation or blurrings of the positions. His 18 chapters, half of them reprinted articles, provide a well-written commentary on the relation of Kohut's theory and practice to the traditional model.

Kohut, having originally tried to locate the self in the ego, id, and superego, gave up the attempt to place or define it. Goldberg goes a little further, suggesting that it is a structure, enduring through time, to be understood in terms of connections, a characteristic configuration, and personal meanings. In its development, a crucial role is accorded to appropriate 'mirroring'; empathic breaks with parents are seen as the prime cause of psychopathology, and their recognition and repair in the analyst's therapeutic mirroring is seen as the work of therapy. Associated with this is the concept of the 'selfobject', by which is meant another person seen as part of, or psychically necessary to, the individual.

As Goldberg points out, these propositions are opposed to or separate from those of classical psychoanalysis, hence the debate. In his view psychoanalytical science is concerned solely with the analytic encounter. This encounter is shaped, observed and reported by the participant analysts and, quite predictably, their descriptions and reports vary enormously between different groups of analysts. The attempt to claim that these disagreements amount to competing paradigms does not hold up. In any case, the field of a given science is defined by its phenomena, not by the observer's favourite instrument, and a scientific psychoanalysis would have to align itself with all the other studies of personal interaction, personality structure, emotion, and so on.

It is likely that the main readership addressed by this book will be relatively unconcerned by the issue of scientific or hermeneutic respectability, but they will be hoping for a full discussion of practices and beliefs. In this respect I found Goldberg's choice of opposition – a loosely identified classical stance – disappointing. How is it that Kernberg gets only two brief mentions and that the British object relations school only rates a brief inaccurate comment on the transitional object, described as "part of an overall, albeit somewhat poorly articulated, theory developed by Winnicott, who was joined later by others such as Guntrip and Fairbairn"? So object relations, splitting, and projective identification – which to my mind can incorporate the ideas encapsulated in the idea of the selfobject and go a long way further, as a key to understanding personality, than does self theory – are entirely ignored.

In the end, we are offered a look at a version of psychoanalysis from one corner of it. Had psychoanalysis been less closed the debate would not have been necessary at all, for the idea of the self has received plenty of attention in other branches of psychology, quite apart from being a dominant concept in literature and in everyday life. Given its curious neglect, we can at least welcome the introduction into psychoanalysis of the view that the central focus of interpretation should be the patient's self-integrity, however slippery the psychoanalytic self continues to be.

ANTHONY RYLE, *Consultant Psychotherapist,*
St Thomas's Hospital, London

The Art of Intervention in Dynamic Psychotherapy. By BERT L. KAPLAN. Northvale, NJ: Jason Aronson. 1988. 263 pp. $25.00.

Psychotherapy trainees and their teachers will find this a valuable book. Trainees are often confused by the variety and complexity of the schools of psychodynamic thought, and at a loss as to how to translate the metapsychological concepts of the differing theories into useful therapeutic interventions with their patients. The book shows how one experienced clinician translates these relatively experience-distant developmental and clinical theories into meaningful, experience-near interventions.

Extensive verbatim transcripts of therapy with seven patients, interwoven with the author's comments, self-analysis, and clinical formulations, are used to show how different perspectives can be applied and integrated to provide a more complete diagnostic picture. It becomes apparent that different theories emphasise different aspects of the patient's experience more than they offer differing explanations.

The major theoretical perspectives which form the book are Hartmann's ego psychology, Mahler's separation individuation developmental model, and Spitz's object relations theory. These provide welcome expositions of significant transatlantic theorists probably unfamiliar to most UK trainees.

The seven cases are described in a clear and lively manner. The author's thought processes and how he combines these with his countertransference responses and knowledge of theoretical concepts to develop emphatic clinical interventions is clearly spelt out. In this respect the book provides a good model for writing up an informative case protocol. Throughout, the author rightly emphasises the need for accurate emphatic understanding as the guiding principle in utilising theoretical constructs.

Trainees should feel reassured having read this book. It will illustrate the complexity and uncertainty of the therapeutic venture, the value of a thorough and eclectic knowledge of theoretical constructs, and a substantial convergence in clinical practice of apparently diverse and at times contradictory theoretical constructs. It would be a useful addition to the trainee psychotherapist's library.

N. D. MACASKILL, *Consultant Psychiatrist, Whiteley Wood Clinic, Woofindin Road, Sheffield*

Families with a Difference: Varieties of Surrogate Parenthood. By MICHAEL and HEATHER HUMPHREY. London: Routledge. 1988. 225 pp. £9.95.

This is a very readable account of the varieties of family life where the genetic link between parents and children is missing or incomplete. Approximately half of the book is devoted to fostering and adoption. As the authors point out, much more has been written about these. However, I was surprised to find that in fact we know very little about foster care, and was left with many questions unanswered. As a society we seem to have placed great faith in foster care on assumptions about the benefits of family life, without comparing this arrangement with normal family life. The chapter on step-parenthood does not involve statutory agencies in their formation, whereas fostering does. There is a chapter on donor insemination, which is followed by an account of new trends in human reproduction. These include *in vitro* fertilisation and surrogacy. The authors then go on to consider what the future may bring on the basis of current scientific developments, e.g. ectogenesis and cloning.

In their opening and final chapters the authors consider whether the nuclear family will survive. Recent changes in reproductive behaviour seem to place this institution under threat. But if we view the family as a social institution, then this book clearly shows that great efforts are being made by many to form this social group either by adoption, fostering, re-marriage, donor insemination, or by taking advantage of recent developments such as *in vitro* fertilisation. The family has survived the changes of the past, and will no doubt survive the changes of today and tomorrow. This book is highly recommended to all those in the helping professions, as some proportion of their clients will be from families with a difference.

NIGEL BEAIL, *Principal Clinical Psychologist and Lecturer in Clinical Psychology, The Keresforth Centre, Barnsley, and the University of Sheffield*

Lithium: Inorganic Pharmacology and Psychiatric Use. Edited by N. J. BIRCH. Oxford: IRL Press. 1988. 288 pp. £35.00.

This publication represents output from the 2nd British Lithium Congress, held in 1987, ten years after the first, and organised largely by Birch and his colleagues from Wolverhampton Polytechnic. Editorial policy was to "allow the whole range of participants … to make brief but adequately documented statements of the recent work in their area", and led to the collection into 14 sections of 90 papers, representing a broad sweep of interests, but inevitably varying considerably in quality.

Reports on clinical studies are concerned with effective serum lithium levels, and with side-effects and their reduction. One of the newer ideas suggests that preparations of the lithium isotope ^{7}Li may produce fewer side-effects than the usually available preparation, which contains both ^{6}Li and ^{7}Li. Such a finding, if paralleled by clinical efficacy, might revolutionise the commercial production of lithium, and bring the economics of lithium therapy into sharper focus than was perhaps intended by one of the contributors. Problems of co-medication, whether with other drugs used in psychiatry or with drugs such as the non-steroidal anti-inflammatory drugs, are considered extensively, as are the absorption characteristics and bioavailability of lithium, knowledge about which is of major importance for a compound whose therapeutic range is narrow and whose toxic effects could be considerable. There are also contributions on the non-psychiatric sequelae of lithium treatment and the effects on the immune system.

A wide range of lithium effects on basic biochemical mechanisms were reported, of which the action on phosphatidyl inositol hypothesis is the most recent development. Both the advice on the administration of lithium to animals and the recognition that intracellular concentrations of lithium are low compared with extracellular levels, should modify strategies adopted in future studies on lithium *in vivo* and *in vitro*.

The book will be of value to the specialist lithium researcher, or to the non-specialist who requires sources which can be followed up in more detail elsewhere, but sadly the reader will obtain little enlightenment on the mysteries of inorganic pharmacology. The presentation is unsatisfactory in that camera-ready copy is only acceptable when it keeps prices down, is well proofread, and editorial control is maintained. None of these conditions seem to have been met here, and the consequence is an uncomfortable book to read.

ELIZABETH F. MARSHALL, *Lecturer in Psychiatric Biochemistry, Department of Psychiatry, University of Newcastle upon Tyne, Newcastle upon Tyne*

Divorce as a Development Process. Edited by JUDITH H. GOLD. Cambridge: Cambridge University Press. 1988. 166 pp. £18.50.

This American book is one of the 'Clinical Insight Series', a series edited by Gold, who also contributes the final chapter of this volume. The series seems designed to produce handbooks on various topics of interest to clinicians working in psychiatry and in other mental health professions. The present volume reviews the effects of divorce on those involved (including children), but it focuses mainly on the therapeutic intervention, "in order to demonstrate ... that marital dissolution can become a catalyst for the individual's subsequent psychosocial growth and development"

This is a multi-author book, and the chapters are diverse. Some are predominantly clinical, looking at, for example, the sexual behaviour of women after divorce, or the impact of divorce on children and adolescents. Some chapters are more to do with the legal processes, and with the sociology of divorce. The statistics quoted at various points are grim: e.g. the fact that there were 1 179 000 divorces in 1983, and the projection that half this year's marriages will end in divorce. Discussion of the economic implications of the 'no fault' divorce brings forth the phrase 'the feminisation of poverty'. Weizman's California study showed that women experienced a drop of 73% in their standard of living by the end of the first post-divorce year. Men gained a 42% rise.

All the chapters in this book offer some interest, and some are thought-provoking, but I feel that this is a book more suited to the general reader than to the experienced clinician. I had hoped that the clinical aspects would offer more, but on the whole I found the therapeutic issues were dealt with rather superficially. There are many case examples, but they gave the impression (no doubt unintentionally) that it is not too difficult to turn the trauma of divorce into a focus for personal development. Mostly the emphasis seems to be on counselling, and even the final chapter, 'Divorce as development: the process of psychotherapy', stresses support, reassurance, and teaching new modes of response. The only discussion of transference and counter-transference issues arises in the chapter 'Assessing and treating divorcing men'. This is by a male therapist, and addresses the male patient:male therapist dyad. Since the book claims to focus on the therapeutic intervention, I think it has fallen short in its examination of its main theme.

I do not believe that this rather expensive little book has much to offer the British specialist reader.

NICOLA BLANDFORD, *Senior Registrar, Department of Psychotherapy, Cambridge*

Psychiatric Interviewing: The Art of Understanding. By SHAWN C. SHEA. Sidcup: Harcourt Brace Jovanovich. 1988. 583 pp. £16.75.

"Sometimes the interviewing process is like exploring a darkened room in an old Victorian house". The author wrote this book as a guide to psychiatric interviewing for mental health workers. He attempts to provide a synthesis of many perspectives. In making this synthesis he undertakes a difficult task, and one might have feared that a poor compromise might be the result. In fact the author has done a good job, and the different viewpoints have been clearly set out.

The first part covers basic principles, focusing on practical issues of sensitive interviewing, such as the patient who refuses shaking hands with the doctor. In the chapter on the treatment plan, Shea stresses the importance of integration and synthesis.

The 'core' of the book contains the application of the fundamentals of interviewing to three of the major psychiatric disorders (depression, psychosis, and personality disorder). The author hopes that interviewing principles in these areas are generalisable to others.

The third part is devoted to special techniques of interviewing. The DSM-III-R criteria have been used for differential diagnosis, keeping the book up to date. It is interspersed with pleasant illustrations of Meg Malloney and quotations from poets such as Emily Dickinson. The author himself writes well. According to Shea interviewing is a shared work of creativity. This is a valuable book both for the novice and the expert.

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Contents of
THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 146, Number 4 **April 1989**

Special articles

435 Genetics and psychiatry: past discoveries, current dilemmas, and future directions. *Herbert Pardes, Charles A. Kaufmann, Harold Alan Pincus and Anne West*
444 Splitting in hospital treatment. *Glen O. Gabbard*
452 Postcardiotomy delirium: conclusions after 25 years? *Lawrence W. Smith and Joel E. Dimsdale*

Regular articles

459 The diagnostic implications of formal thought disorder in mania and schizophrenia: a reassessment. *V. Chowdary Jampala, Michael Alan Taylor and Richard Abrams*
464 Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. *Richard L. Suddath, Manuel F. Casanova, Terry E. Goldberg, David G. Daniel, John R. Kelsoe, Jr and Daniel R. Weinberger*
473 HPA axis hyperactivity and recovery from functional psychoses. *William H. Coryell and Mark Zimmerman*
478 Clinical status and emotional adjustment of children of depressed mothers. *Catherine M. Lee and Ian H. Gotlib*
484 Life events of adolescents in relation to personal and parental substance abuse. *Sandra A. Brown*
490 Childhood trauma in borderline personality disorder. *Judith Lewis Herman, J. Christopher Perry and Bessel A. van der Kolk*
496 Personality disorder in the families of depressed, schizophrenic, and never-ill probands. *William H. Coryell and Mark Zimmerman*
503 The DST in children and adolescents with major depressive disorder. *Charles D. Casat, George W. Arana and Karin Powell*
508 Ability to form an alliance with the therapist: a possible marker of prognosis for patients with antisocial personality disorder. *Linda Gerstley, A. Thomas McLellan, Arthur I. Alterman, George E. Woody, Lester Luborsky and Maurice Prout*

Brief Communications

513 A controlled trial of desipramine in 18 men with posttraumatic stress disorder. *Christopher Reist, Curtis D. Kaufmann, Richard J. Haier, Christopher Sangdahl, Edward M. DeMet, Aleksandra Chicz-DeMet and James N. Nelson*
517 Infrequent occurrence of EEG abnormalities in panic disorder. *Murray B. Stein and Thomas W. Uhde*
521 Psychosis, aggression, and self-destructive behaviour in hospitalized adolescents. *Isabelle Delga, Robert K. Heinssen, Richard C. Fritsch, Wells Goodrich and Brian T. Yates*
526 High prevalence of visual hallucinations in research subjects with chronic schizophrenia. *H. Stefan Bracha, Owen M. Wolkowitz, James B. Lohr, Craig N. Karson and Llewellyn B. Bigelow*
529 Benzodiazepine dependence and withdrawal in elderly patients. *Edward Schweizer, W. George Case and Karl Rickels*

Clinical and Research Reports

532 A magnetic resonance imaging study of autism: normal fourth ventricle size and absence of pathology. *H. Jordan Garber, Edward R. Ritvo, Lee C. Chiu, Virginia J. Griswold, Alona Kashanian, B. J. Freeman and William H. Oldendorf*
534 Seasonal cocaine abuse. *Sally L. Satel and Frank H. Gawin*
536 Carbamazepine treatment for benzodiazepine withdrawal. *Richard K. Ries, Peter P. Roy-Byrne, Nicholas G. Ward, Vernon Neppe and Sam Cullison*
538 Behavioral hyporeactivity to physostigmine in detoxified primary alcoholics. *David S. Janowsky, S. Craig Risch, Michael Irwin and Marc A. Schuckit*

Contents of The Journal of Nervous and Mental Disease

April 1989 **Volume 177, Number 4**

Type A behavior and the social production of cardiovascular disease. *William W. Dressler* 181

Psychopathology and social functioning in women with Turner syndrome. *Jennifer Downey, Anke A. Ehrhardt, Rhoda Gruen, Jennifer J. Bell and Akira Morishima* 191

Anxiety disorders among Mexican Americans and non-Hispanic whites in Los Angeles. *Marvin Karno, Jacqueline M. Golding, M. Audrey Burnam, Richard L. Hough, Javier I. Escobar, Kenneth M. Wells and Richard Boyer* 202

Depression, pain, and hemispheric activation. *Michael W. Otto, Michael J. Dougher and Ronald A. Yeo* 210

Two syndromes of schizophrenic psychopathology associated with left vs. right temporal deficits in P300 amplitude. Four case reports. *Martha E. Shenton, Ruth Ballinger, Brian Marcy, Steven F. Faux, Melanie Cane, Margorie Lemay, Geraldine Cassens, Michael Coleman, Frank H. Duffy and Robert W. McCarley* 219

Computed tomography findings in delirium. *Hannu Koponen, Leevi Hurri, Ulla Stenbäck, Esa Mattila, Hilkka Soininen and Paavo J. Riekkinen* 226

Obsessive-compulsive disorder in mentally retarded patients. *Benedetto Vitiello, Scott Spreat and David Behar* 232

Correlates of memory in Parkinson's disease. *Manuel Riklan, Constance M. Reynolds and Stanley Stellar* 237

Index to Advertisers

harmaceuticals

he Boots Company plc .... *facing* p 628

onvaTec Ltd. (Squibb) .... p x

'uphar Laboratories Limited .... *facing* p 634

li Lilly .... *facing* p 628

undbeck Limited .... p ii & outside back cover

. Merck Ltd. .... *facing* p 629

ooksellers and Publishers

hurchill Livingstone ....p viii

linics, Hospitals and Nursing Homes

t. Andrew's Hospital .... *facing* p 635

evern Clinic ....p ix

avistock Clinic .... p vii

Appointments

Abbotsford General Hospital ....p vi

Lord Chancellor's Office .... p vii

Royal Alexandra Hospitals ....p iv

Miscellaneous

Institute of Family Therapy ....p iv

Kuoni Travel ....p iv

Royal College of Psychiatrists .... p v

Royal College of Psychiatrists ....p vi

School of Hypnosis & Advanced Psychotherapy .p vi

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DEPRESSION AND REVERSIBLE MONOAMINE OXIDASE INHIBITORS– NEW PERSPECTIVES

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R. G. Priest

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R.G. PRIEST

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Contents

List of Contributors 4
Supplement Policy of the Journal 6

Editor's Preface: Antidepressants of the future
R.G. PRIEST 7

A European study of views on the use of monoamine oxidase inhibitors
E.S. PAYKEL and J.L. WHITE 9

The genetics of depression: Current approaches
P. McGUFFIN and R. KATZ 18

Suicide and antidepressant overdosage in general practice
G. BEAUMONT 27

Tyramine and new monoamine oxidase inhibitor drugs
G.M. SIMPSON and J. DE LEON 32

Tyramine and irreversible monoamine oxidase inhibitors in clinical practice
A.J. COOPER 38

Antidepressants in panic disorders
M.R. LIEBOWITZ 46

Biochemical aspects of the pharmacology of moclobemide: The implications of animal studies
B.A. CALLINGHAM 53

Effect of a reversible monoamine oxidase-A inhibitor (moclobemide) on sleep of depressed patients
J.M. MONTI 61

The pharmacology of reversible monoamine oxidase inhibitors
R. AMREIN, S.R. ALLEN, T.W. GUENTERT, D. HARTMANN, T. LORSCHEID, M.-P. SCHOERLIN and D. VRANESIC 66

A double-blind comparative trial of moclobemide v. imipramine and placebo in major depressive episodes
M. VERSIANI, U. OGGERO, P. ALTERWAIN, R. CAPPONI, F. DAJAS, G. HEINZE-MARTIN, C.A. MARQUEZ, M.A. POLEO, L.E. RIVERO-ALMANZOR, L. ROSSEL, W. SCHMID-BURGK and R. UCHA UDABE 72

Efficacy and tolerability of moclobemide compared with imipramine in depressive disorder (DSM-III): An Austrian double-blind, multicentre study
U. BAUMHACKL, K. BIZIÈRE, F. FISCHBACH, Ch. GERETSEGGER, G. HEBENSTREIT, E. RADMAYR and M. STABL 78

Pre-clinical pharmacology of moclobemide: A review of published studies
W. P. BURKARD, M. DA PRADA, H. H. KELLER, R. KETTLER and W. HAEFELY 84

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Supplement Policy of the Journal

H.L. FREEMAN

At the request of the College's Executive & Finance Committee, I am pleased to take this opportunity to clarify the arrangements for publishing the *Journal's* supplements, in case these should have given rise to any misconceptions. It was agreed by the College Council that a supplement policy should be inaugurated, in line with the practice of a number of other leading journals. Stringent requirements were laid down for ensuring the scientific quality of material to be published in this way, and for maintaining the *Journal's* total editorial control of it; these requirements have been scrupulously followed. The present supplement is the sixth to be issued so far in a two-year period, and the programme has allowed a very substantial additional amount of important scientific information to be published. Because of the heavy and constantly growing pressure on the *Journal's* space — with submissions increasing annually at 5–10% — this is a very necessary additional vehicle for authors, notwithstanding that the *Journal* itself has increased substantially in size.

However, because supplements are expensive to produce, this *Journal* — like all others — must find a partner or sponsor in each case, to allow for their publication. So far, these have included the World Health Organization, the Basque Regional Government, the University of Bern, and several international pharmaceutical companies. In a number of cases, the papers published in a supplement have been derived from those delivered at a meeting with which one of these organisations has been associated in some way. However, the choice of material to be published and its editing are wholly and exclusively in the hands of the *Journal*, and the fact that a paper has been delivered at such a meeting means only that it is available to be considered for publication. Papers considered in this way are subject to a stringent peer-review process and detailed scientific editing, in accordance with the *Journal's* normal practice, as will be evident in the high quality of material that has so far appeared in the supplements.

Where publication has been assisted by a pharmaceutical company, this may be simply part of its support to professional education, or the supplement may contain one or more papers relating to a drug produced by that company. (In that case, the drug may or may not be on the market in the United Kingdom or other countries.) In the latter circumstances, no company has ever sought to influence in any way the process by which papers are selected or edited, and no such influence would ever be entertained by the *Journal*.

It is clearly in the interests of both clinicians and scientific workers that they should be fully and quickly informed of new data relating to drugs which may be of clinical importance. The supplement programme makes a useful contribution to that task, and does so in a way which ensures the reliability of the published material.

In the same way that companies may distribute reprints of individual papers from journals which refer to one of their products, they may well wish to do so in the case of a supplement which does the same. The role of the *Journal* is simply to guarantee the scientific quality of the material published. It does not 'endorse' a drug referred to in a supplement, any more than it does so in the case of a drug mentioned in a normal *Journal* paper. No suggestion to that effect has ever been made with the authority of any pharmaceutical company.

I have been much encouraged by the balance of opinion received on the *Journal's* supplement programme up to now, and I am confident that the series will continue to maintain an equally high scientific standard in the future.

H.L. Freeman, *Editor, British Journal of Psychiatry*

British Journal of Psychiatry (1989), **155** (suppl. 6), 7–8

Editor's Preface
Antidepressants of the Future

R.G. PRIEST

Existing antidepressants are unsatisfactory: they have limited efficacy, side-effects are a problem, and there is an appreciable degree of toxicity. However, non-pharmacological, psychological approaches to the treatment of depression also have their own drawbacks, so that the search for better antidepressant compounds continues.

Limitations of efficacy

The efficacy of antidepressants is limited in several ways. In the first place, it cannot accurately be predicted who will respond, either to physical methods of treatment in general, or to any class of antidepressant in particular. Clinicians are familiar with the necessity of waiting for two weeks or so for the effect of treatment to begin to reveal itself, and in addition, there is a substantial proportion of patients who fail to respond to any active drug.

There is also a curious tendency for active drugs to be equipotent in any one investigation. When a three-way trial is carried out on two active drugs (A and B) and on a placebo control (C), then it is repeatedly found that although both the active drugs are superior to the placebo, there is no significant difference between the two active compounds (Fig. 1). Does this mean that there is a natural, built-in limit to the efficacy of an antidepressant drug? Does it mean that there is a psychopharmacological on–off mechanism – that a new drug either works or it does not, with no possibility of it being superior in efficacy to existing compounds?

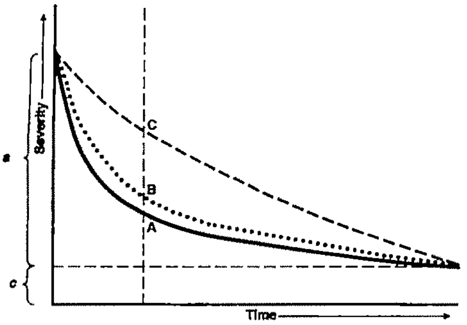

FIG. 1 Comparison of the efficacy of two inactive drugs (A and B) and placebo (C) with time.

There are, in fact, alternative explanations. The simplest of these is that the findings are artificial results of our analysis. This can be illustrated with another problem, which is frequently found in drug trials. An early difference between active drug and placebo often seems to disappear on prolonged follow-up. For instance, the effect of a drug, compared with placebo, can be shown to be significantly superior at four to six weeks, but after six months the difference is no longer statistically significant. This should no longer surprise us, though, for the following reasons.

The curves of improvement that are often obtained with trials of antidepressant drugs approximate to exponential decay curves of the general formula $y = e^{-x}$, or more particularly $y = ae^{-bx} + c$ (Fig. 1).

The larger the number of patients, the closer the curves come to fit this theoretical distribution. Inspection of perfect mathematical exponential curves, starting from an identical origin on the y axis, shows that initially they will diverge, but eventually will converge as they approach infinity. Thus, using the raw data, there is bound to be an optimum place on the x axis where the two curves are furthest apart, and where the difference is most likely to be significant.

An alternative method of analysis would be to take the logarithms. The curves then become straight lines, and the formula reduces to $\log (y-c)=(\log a)-bx$. The slope of the line is given by $-b$. This is then a single figure that makes use of all the data points on the curve, and would provide a powerful and stable indicator of the *rate of improvement* which is characteristic of the treatment in question. From the clinical point of view, that is what we are most interested in discovering.

However, these curves are based on the average scores from large numbers of patients, and there are many individuals whose progress follows quite a different path. On any given treatment, a significant number do not improve at all, while others improve at an unacceptably slow pace.

Thus, it is important to continue looking for new treatments that might be more effective for a given individual.

Side-effects and toxicity

We cannot remain indifferent to the serious side-effects of antidepressants, such as tricyclics. The parasympathetic blockade that they produce carries with it not just nuisance value for the patient, but also potential morbidity and loss of compliance, as well as toxicity in overdose (including cardiac effects).

For their part, traditional monoamine oxidase inhibitors (MAOIs) are sometimes unpleasant to take, and there is a surprising degree of resistance on the part of patients to the limitations required with them.

The novel antidepressants (non-tricyclic, non-MAOI) are still in the process of evaluation, but some (e.g. nomifensine, zimelidine) have already had to be withdrawn because of toxicity. Thus, we are still searching for antidepressants that are more acceptable and safer than the original ones.

It is the opinion of most doctors who work with depressed patients that antidepressant drugs are of inestimable value in clinical practice. However, they would like to have compounds that are more efficacious and less toxic than those currently available and, in addition, they hope to have antidepressant drugs that will help those patients who are now classified as suffering from 'resistant' or 'chronic' depression.

New MAOIs

The papers that follow provide a useful opportunity to reassess the roles of antidepressants in general, of tricyclics, of traditional MAOIs, and of newer drugs, particularly the selective and reversible MAOIs (Nutt & Glue, 1989).

One of the most interesting of the last seems to be moclobemide. Its relatively brief pharmacological action is due to the fact that the enzyme is not permanently inhibited, as it is with the older MAOIs. This drug has a relatively short plasma half-life and when it reaches the tissues, local breakdown ensures a short half-life there also. If a large amount of tyramine is ingested, it may be degraded as a result of mass action. Possibly because of moclobemide's selectivity, there could also be deamination of the tyramine by MAO-B.

Empirically, moclobemide appears to be well tolerated compared with older drugs, and compliance with it may therefore be expected to be relatively good. Unlike other MAOIs, it has a side-effect profile similar to that of 'novel' antidepressants such as mianserin, trazodone, viloxazine, and the serotonin (5-HT) re-uptake inhibitors fluoxetine and fluvoxamine, none of which are either tricyclics or traditional MAOIs (Benfield & Ward, 1986; Priest & Woolfson, 1986). The unwanted effects of these newer drugs seem to consist of five principal symptoms: dizziness, nausea, headache, drowsiness, and insomnia.

Whilst the papers in this supplement are all original, it should be noted that the contribution by Burkard *et al* consists of a review of published studies on the preclinical pharmacology of moclobemide. It is hoped that this will be of considerable value to those who may not have access to the original sources of the material on this subject.

The main conclusion to be drawn from these papers is that the stereotype of MAOIs, which goes along with dietary restrictions, the 'cheese effect', permanent inactivation of the enzyme, and the target syndrome of 'atypical' depression, should be discarded. Instead, we can now think in terms of a new class of antidepressants – one that may perhaps deserve the description of the 'gentle MAOIs'.

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A European Study of Views on the Use of Monoamine Oxidase Inhibitors

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A total of 1269 psychiatrists, from 15 European countries, completed a questionnaire assessing treatment choice in depressive and anxiety disorders, with particular focus on diagnostic and other factors determining use of monoamine oxidase inhibitors (MAOIs). Tricyclic and similar antidepressants were used most commonly — MAOIs were used as first-choice therapy for depressive or anxiety disorders only by a minority but were commonly a second-choice treatment for atypical depressives. Use was inhibited by interactions and side-effects rather than by perceived ineffectiveness. Cross-national differences in treatment were considerable but diagnostic differences in case history vignettes were much smaller.

Although there has been 30 years of experience with the monoamine oxidase inhibitors (MAOIs), their exact role in clinical psychiatry has remained unclear. Introduced in the late 1950s and initially heralded as effective drugs in the treatment of depression, their rapid fall from favour reflected a number of problems. Most notable was the recognition of the 'cheese' reaction (Blackwell, 1963), which led to concerns over toxicity and a subsequent need for dietary restrictions with prescribing. These fears were later compounded by unfavourable reports on efficacy, generated by a number of multi-centre trials (Greenblatt *et al*, 1964; Medical Research Council, 1965; Raskin *et al*, 1974). Prescribing of the MAOIs was in general limited to a minority of protagonists who continued to advocate their efficacy, with somewhat greater use in the UK than elsewhere.

A review by Tyrer (1976) predicted a potential revival in the prescribing of MAOIs and drew attention to studies suggesting their efficacy in anxiety (Tyrer *et al*, 1973). The view that these drugs are effective in specific groups goes back to Sargant and his colleagues (e.g. West & Dally, 1959), who first delineated the concept of atypical depression. In this and subsequent papers, they described a diverse group of features, including presence of anxiety, 'atypical functional shift' symptoms (increased sleep, increased appetite, evening worsening), as well as other features of non-endogenous depression (Paykel *et al*, 1983). More recent controlled studies showing that MAOIs are clearly superior to placebo have suggested selectivity in the direction of anxiety (Ravaris *et al*, 1980; Paykel *et al*, 1982), atypical functional shift (Liebowitz *et al*, 1984), or more recently, the combination of the two (Davidson *et al*, 1988; Liebowitz *et al*, 1988).

In parallel to these clinical studies, psychopharmacological research has uncovered the isoenzyme A and B forms of monoamine oxidase: MAO-A and MAO-B. This has led to the development of selective MAOIs. Specific MAO-B inhibitors appear to have limited use in depression, although they are being used with some success in Parkinson's disease. More recently, a new group of drugs has been developed, such as moclobemide and brofaramine, which are not only highly selective for MAO-A, but are also reversible in action, and thus have a much improved safety profile.

In the light of these developments, it seemed timely to evaluate the current status of MAOI prescribing in Europe.

The aims of the European study of MAOIs were to examine current national prescribing trends of both MAOIs and other psychotropics, and to evaluate the factors perceived as important in the decision to prescribe. In addition, the study aimed to investigate attitudes to the older drugs and to evaluate the potential role for a new MAOI.

Method

Logistical problems and the wide geographical spread of the proposed sample precluded the use of any survey method which required face-to-face interviewing; a questionnaire was therefore chosen as the only practical option. Given this decision, the issue of the type of stimulus material to be used to elicit treatment responses needed to be resolved. The problems of designing and evaluating such survey material have been well described by Hall *et al* (1982) in their report on the Quality Assurance in Aspects of Psychiatry Project in Australia and New Zealand. Our questionnaire design was, in part, based on the methods previously evaluated within that project.

The chosen design incorporated two approaches: a fixed-choice selection of treatment in response to a given diagnosis, and treatment selection in response to three case vignettes. In the latter instance, open-ended questions on diagnosis were included.

To avoid diagnostic confusion, particularly as the survey was across national boundaries and because MAOIs are often prescribed for a group of disorders which are not necessarily well-described within standard diagnostic classifications, working diagnoses (outlined in a glossary) were used throughout the questionnaire (Table I). This was piloted in 1988 and was completed by 118 respondents, representing a mixed sample

TABLE I
Psychiatric classification

A. *Neurotic/reactive depression*
Depression without psychotic or biological symptoms, which is related to current life circumstances, although disproportionate in extent
B. *Endogenous depression*
(I) Widespread depressed mood with biological symptoms and psychomotor agitation
(II) Widespread depressed mood with biological symptoms and psychomotor retardation
C. *Atypical depression*
(I) Depression with atypical symptoms such as weight gain and increased sleep
(II) Depression with anxiety and/or phobic symptoms
D. *Anxiety neurosis*
Generalised, persistent anxiety with autonomic symptoms
E. *Panic disorder*
Presence of panic attacks, i.e. episodes of severe anxiety with autonomic symptoms
F. *Agoraphobia*
Intense fear and avoidance of being in public places
G. *Other phobias*
Avoidance of other specific objects or situations due to an irrational fear
H. *Bulimia*
An eating disorder with binge eating and vomiting
I. *Personality disorder*
Deeply ingrained maladaptive patterns of behaviour

of practising psychiatrists throughout Europe. This preliminary questionnaire was presented in English; minor revisions were subsequently made.

The final questionnaire contained 42 questions. The first section required fixed-choice responses to diagnosis-related questions on the treatment of anxiety and depressive disorders and on the frequency of use of categories of psychotropic drugs. The second section elicited fixed-choice responses to questions regarding respondents' views on prescribing of antidepressants in general, and of MAOIs in particular. The latter section presented three short case vignettes, chosen to represent both classical and atypical depressive and anxiety disorders. No diagnoses were assigned to these cases. Respondents were asked for their own diagnosis.

The questionnaire concentrated on drug treatment and stated this bias within the preface, although acknowledging the value of psychotherapy and allowing for its inclusion as a treatment modality within each section as an item entered as 'other'.

To overcome the problem of language difficulties, the questionnaire was published in five language editions – English, French, German, Spanish and Italian – and distributed as appropriate during December 1988 to 17 417 psychiatrists throughout Europe.

The sample

The sample of practising psychiatrists was defined through medical mailing lists within each country and included all senior and junior psychiatrists registered on those lists. A single mailing was sent out. Due to the very large scale of the project, no follow-up mailing or follow-up of non-responders was undertaken.

Data coding and analysis

All questionnaire responses were coded for analysis: for the open-ended questions, categories were evolved as coding proceeded. A preliminary set of codes was evaluated from the pilot study and in most instances, these were representative of the categories subsequently designated. Where this was not possible, a new category was created.

Results

Sample characteristics

The final number of respondents (cut-off date February 1989) was 1314; of these, 1269 were evaluable. The breakdown of responses per country and the percentage response are shown in Table II. Overall, there was a 7.54% response to the questionnaire, with the highest percentage responses in the UK (12.6%) and Ireland (13.5%).

Demographic data showed that the sample had a median number of 13 years' experience in psychiatry (range 2–30+) and a median practice size of 60 in-patients and 132 out-patients, although the range was extremely broad. Outside the UK, there was an increased number of responders reporting an out-patient only service and a higher proportion from private practice, reflecting current practice within each country.

Treatment of depressive disorders

The first section of the questionnaire elicited fixed-choice responses to questions regarding current prescribing habits in depressive disorders. Respondents were asked to rate first and second choice of treatment to a range of disorders, classified according to the glossary. Second-choice therapy was defined as that which would be selected following initial treatment failure. Taking the first choice of treatment, the overall results are illustrated in Fig. 1, which shows selected treatments for the whole sample. From this, it can be seen that the tricyclics (TCAs) were selected as first-choice treatment across the whole range of disorders specified. This held true for all countries

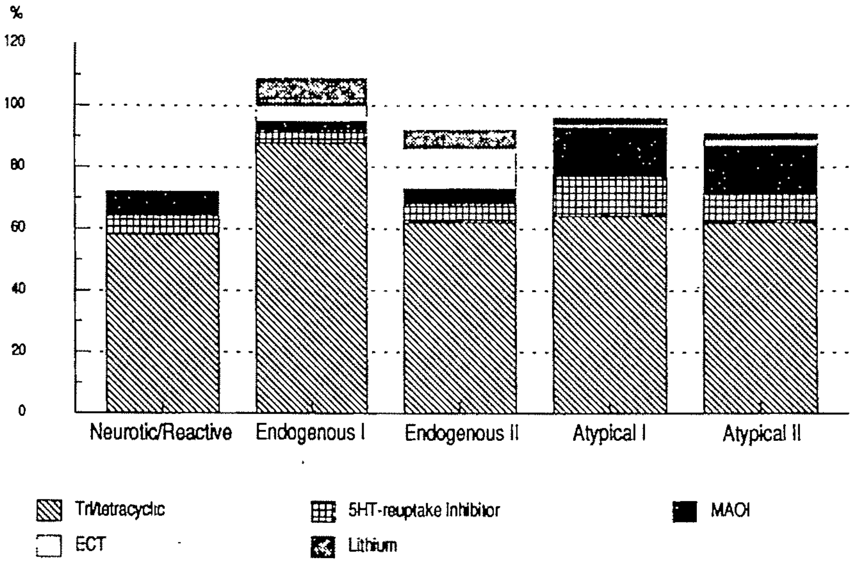

FIG. 1 First choice in the treatment of depressive disorder.

TABLE II
Questionnaire distribution and responses

Country	*Responses*	*Responses (of total no. distributed) (%)*
UK	482	12.6
Ireland	23	13.5
France	195	6.4
Belgium	71	8.7
Netherlands	68	5.0
Italy	141	4.5
Spain	37	3.9
Portugal	10	3.9
Germany	68	5.4
Switzerland	62	7.7
Austria	16	8.2
Denmark	32	6.3
Finland	24	7.4
Norway	24	4.6
Sweden	61	7.5
	1314	7.54

and was most marked for the endogenous depressions, particularly for agitated depression, where 84–100% of respondents selected tricyclics as a first choice. Similarly, ECT was selected primarily for endogenous depression – by 5% for agitated endogenous depression; 13% in retarded endogenous depression. It was selected as first choice most frequently in the UK, France, Norway, and Sweden, and was a low choice priority in Switzerland, The Netherlands, Italy, Germany, and Belgium.

With regard to the spread of responses and to international prescribing differences, neurotic depression elicited the most mixed response. Here again, TCAs were most frequently selected as first choice, but the spread of selected therapies was wider. Psychiatrists in France, Switzerland, and The Netherlands more frequently selected serotonin (5-HT) reuptake inhibitors. MAOIs were selected more frequently in the UK, Ireland, and Spain. Psychotherapy was selected as an alternative by 10–15% of respondents, predominantly in Germany, the UK, and The Netherlands.

Looking more specifically at the use of the MAOIs in depressive disorders, the spread of prescribing as first-choice therapy is illustrated in Table III. The frequency of MAOI prescribing as second choice of therapy was 22% for neurotic reactive depression, 13% and 12% for endogenous depression (I) and (II) respectively, and 27% and 26% for atypical depression (I) and (II) respectively.

In both instances, prescribing was higher in the case of neurotic and atypical depressions and greater in certain countries – namely, the UK, Spain, and Ireland. In atypical depression, an overall 15% of respondents selected an MAOI as treatment of first choice. This figure rose to 27% when second choice of treatment was considered, and this represented a predominant choice from those selecting a TCA as first-choice therapy. Only 3% of respondents selected an MAOI as both first and second choices in any disorder. Thus, an overall 42% of respondents selected an MAOI as first- or second-choice treatment in atypical depression.

In three questions, respondents were asked which specific antidepressants and other psychotropics they currently used: the results for the non-MAOI antidepressants are shown in Table IV. Some drugs are used more frequently in certain

TABLE III
Percentage of respondents choosing MAOIs as first-choice therapy in the following disorders

	Total no. (%)	*Switzerland (%)*	*UK (%)*	*France (%)*	*Italy (%)*	*Spain (%)*	*Scandinavia (%)*	*Germany (%)*	*Netherlands (%)*
Neurotic/ reactive depression	8	0	12	8	8	32	0	2	0
Endogenous depression (I)	3	0	1	5	4	10	0	9	0
Endogenous depression (II)	6	0	1	13	8	10	3	0	2
Atypical depression (I)	15	2	24	14	9	19	6	9	2
Atypical depression (II)	15	2	27	6	9	19	3	16	3

TABLE IV
Current frequency of use of non-MAOI antidepressants

	(%)		(%)
Amitriptyline	86	Desipramine	20
Clomipramine	79	Viloxazine	19
Imipramine	69	Amineptine	14
Mianserin	53	Protriptyline	9
Dothiepin	49	Fluoxetine	8
Maprotiline	43	Opipramol	8
Lofepramine	41	Melitracen	7
Fluvoxamine	40	Amoxapine	6
Doxepin	34	Other	4
Trimipramine	33	Butriptyline	2
Trazodone	30	Iprindole	1
Nortriptyline	26		

countries: e.g. maprotiline scored highly in Belgium, Germany, France, Switzerland, and The Netherlands; dothiepin scored highly in Belgium and Ireland; amoxapine in Denmark, France, and Spain, and doxepin in Germany.

The use of MAOIs reflected the variable availability of these drugs. Generally, phenelzine is the most frequently prescribed, except in France and Germany, where the newer MAOI, toloxatone was cited as first choice.

A number of other drugs are also being used in depression. Analysis of cross-national prescribing showed that the use of alprazolam was high in Italy, Spain, and Sweden, flupenthixol is frequently prescribed in Scandinavia, sulpiride in Belgium, France, and Italy, and L-tryptophan in the UK. Lithium was most frequently used in the UK and Scandinavia.

Treatment of anxiety disorders

The overall results for first choice of therapy in the anxiety disorders are shown in Fig. 2. Benzodiazepines were the most frequently selected treatment for anxiety neurosis (47%) while TCAs predominated in panic disorder and agoraphobia. The use of MAOIs as first-choice treatment in these disorders was relatively low, with a small trend towards more frequent selection in agoraphobia. In general, a broader range of treatments was selected in anxiety, compared to the depressions, and some marked variations, both within and between countries, were revealed.

In anxiety neurosis, the use of benzodiazepines was high in Italy, Spain, and France, and low in the UK, Germany, and Denmark. MAOIs had their largest group of users in the UK, where 9% entered them as drugs of first choice. Of the other drugs, major tranquillisers scored highly in Scandinavia (24%). Beta-blockers were used by a significant group in Germany (13%).

In panic disorder, the treatment of first choice was split between benzodiazepines and TCAs, with benzodiazepines predominating in Belgium, Italy, and Switzerland, and TCAs in the UK and Scandinavia; 5-HT re-uptake inhibitors had a significant score in The Netherlands. Again, the highest MAOI users were clustered in the UK (13%) and Ireland (13%), but also, in this instance, in Germany (11%).

MAOI indications

The next section of the questionnaire endeavoured to examine which clinical symptoms are perceived by the practising psychiatrist to be responsive to MAOIs. Of the total sample, 47% said that they did choose an MAOI on the basis of certain symptoms or symptom groups. This percentage was slightly greater in the high-user countries (64% in the UK for example). There was a particularly low response in Switzerland (16%) and The Netherlands (15%).

Those respondents who answered "yes" were then asked to rank a selection of five symptoms (from a list of 22 items) from 1 to 5, where 1 rated as the most responsive to an MAOI and 5 the least. The highest ranked symptoms were psychomotor retardation (2.1), panic episodes (2.4), lethargy and fatigue (2.5), agoraphobia (2.7), reactivity of mood (2.7), and

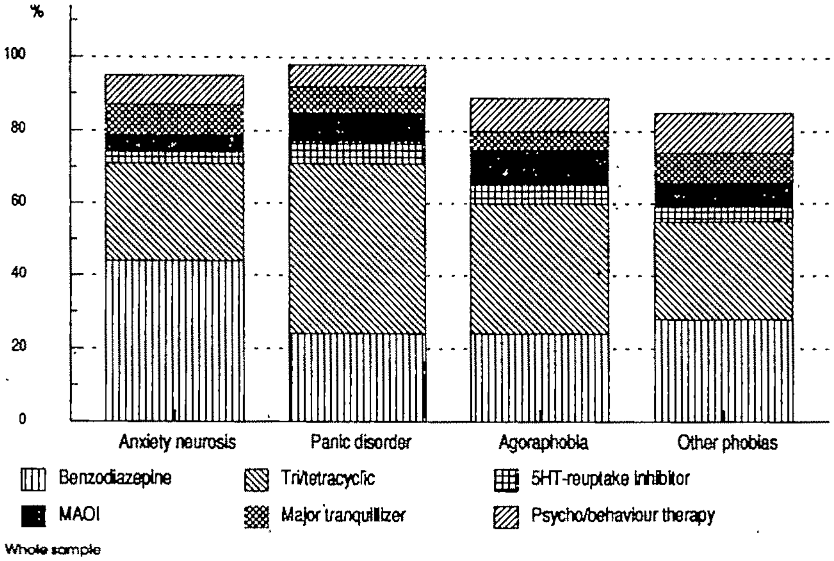

Fig. 2 Treatment of anxiety.

hypersomnia (2.7). An interesting variation emerged when cross-country responses were considered for the first item — psychomotor retardation (Table V). For this item, there was a significant difference in ranking between the high- and low-user countries, with high users ranking this item almost zero. The difference appeared to reflect the divergence between the two views of the nature of retardation, with psychiatrists from one group of countries regarding it as an aspect of endogenous depression and a contra-indication to MAOIs, the other as an aspect of fatigue, and therefore an indication.

Looking more specifically at item ranking in the UK, panic episodes were ranked highest (2.2), followed by reactivity of mood (2.4), hypersomnia (2.5), agoraphobia (2.6), lethargy and fatigue (2.7), poor response to ECT (2.7), and hyperphagia (3). Two clusters of items were highlighted — one characteristic of reversed functional shift, and the other of anxiety.

What are the disadvantages of MAOIs?

Respondents were asked to indicate disadvantages of current MAOIs and potential advantages of a new drug. There was a clear uniformity of response across the countries.

Table V
Psychomotor retardation: respondents indicating as most responsive to MAOIs (%)

UK	1	Italy	32
Belgium	39	Netherlands	10
Denmark	6	Norway	0
France	42	Switzerland	44
Germany	65	Spain	0
Ireland	6	Sweden	18

The disadvantages cited for the MAOIs, in descending order of ranking, were potential drug interactions, interactions with tyramine in food, side-effects, toxicity in overdose, need for patient counselling, problems relating to anaesthesia, delay in onset of action, lack of efficacy, and stimulating effect. Lack of efficacy was thus not ranked as an important disadvantage. In high-user countries, however, the cheese reaction was ranked above drug interactions. In a new MAOI, respondents are looking for, in descending order of ranking, increased efficacy over other available antidepressants, absence of food interactions, fewer side-effects than available antidepressants, absence of drug interactions, lower toxicity in overdose than other antidepressants, faster onset of action, no anti-cholinergic side-effects, and lack of sedative effects. Again, there were no clear cross-national differences in response to these questions.

Efficacy of MAOIs

Looking more closely at efficacy, the next question was concerned with the perceived efficacy of MAOIs, as judged by the literature. The percentage of respondents indicating that they considered the literature to demonstrate efficacy clearly in each disorder is shown in Fig. 3, which gives the results for the group overall. When these were analysed per country, no significant differences emerged. A surprising result in this section is the high scores for endogenous depression: over 80% of respondents from Belgium and Denmark, for example, indicated that in their view, the literature showed clear evidence of efficacy in both endogenous depression I and II. There was a slight trend towards a higher response from high prescriber countries for atypical depression, panic disorder, and agoraphobia.

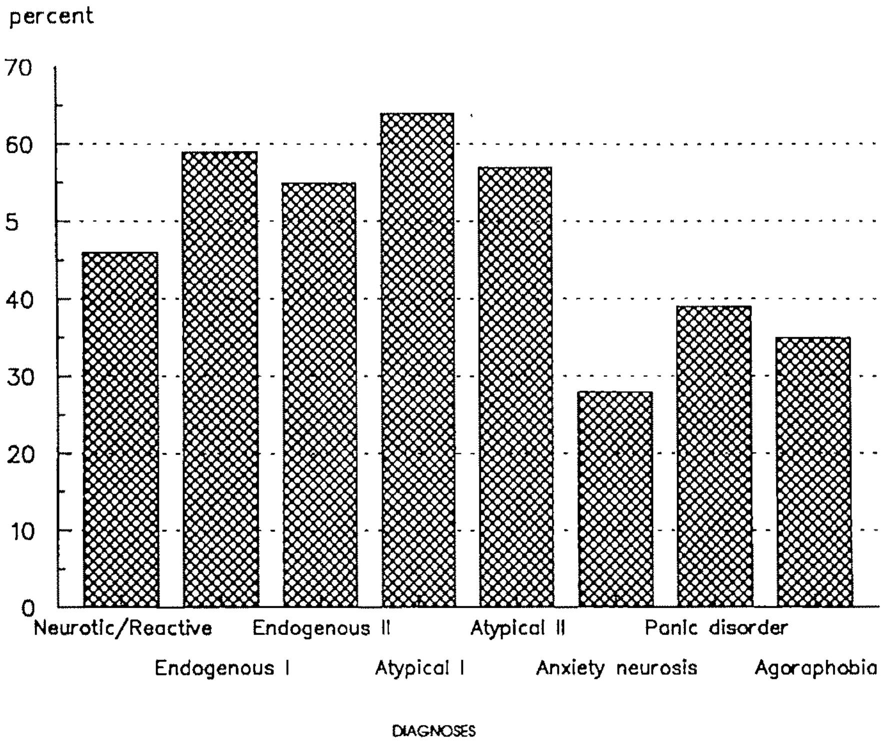

FIG. 3 Respondents indicating clear evidence of efficacy for MAOIs.

Comparing these responses to frequency of prescribing, approximately 25% of those indicating evidence for efficacy in each disorder stated that they never prescribe MAOIs. This anomaly is partly explained by the disadvantages reported in the earlier section, which were confirmed by asking what were the actual reasons for not prescribing.

Respondents were asked about some additional reasons for not prescribing. Proportions who would never prescribe were for suicide risk (46%), history of alcohol abuse (57%), history of drug abuse (64%), history of self-destructive behaviour (49%), history of impulsivity (57%), and low intelligence (59%).

In some additional clinical situations, a high percentage of respondents stated that they would avoid MAOIs: hypertension (66%), post-myocardial infarction (55%), liver disease (61%), likelihood of operation (68%), pregnancy (77%), and low intelligence (48%).

When asked if the introduction of a new, safer MAOI would change their prescribing habits, an overall 71% indicated that they would prescribe a new MAOI in preference to an older drug, and would then extend their prescribing of MAOIs. A total of 68–78% of respondents indicated that they would increase prescribing from between 5–20% in depressive disorders and over 80% would increase prescribing similarly in anxiety disorders.

Responses to case vignettes

In this section, three case histories were presented (Table VI). Respondents were asked if they would consider drug therapy as part of the treatment plan, and were then asked to select a first choice of treatment, as well as a second choice in the event of treatment failure. Finally, an open-ended question asked for the diagnosis.

Analysis of the diagnoses assigned to Case 1 showed a range of diagnostic labels (Table VII), all within the anxiety spectrum and focusing on agoraphobia and panic. Cross-national differences were not marked, but the UK, Germany, and Switzerland tended to prefer agoraphobia; France, phobic neurosis or disorder; and The Netherlands and Sweden, panic disorder.

For this case, 75% indicated that they would use drug therapy as part of the treatment plan. The drugs of first- and second-choice are shown in Table VIII. The most frequently selected treatment was with the TCAs/tetracyclics. A smaller, but significant, percentage chose an MAOI and a smaller group selected a 5-HT re-uptake inhibitor. The majority of the MAOI prescribers were from the UK, Ireland, and Germany. Benzodiazepine prescribing was high in Italy and Belgium. Second-choice treatment strategies showed a swing to the MAOIs, again highest in the UK. The high percentage of

TABLE VI
Case vignettes

Case 1

A 38-year-old man with a 3-year history of fear of leaving the house. Severe anxiety before he has to leave the house, with tremulousness and palpitations. On at least 10 occasions has experienced sudden severe anxiety attacks in the street, with fear of death, chest pain, palpitations, sweating, and tremulousness. Some associated depressed mood; no change in sleep, appetite, weight or energy levels. No suicidal ideas. Conscientious, dependent personality.

Case 2

A 25-year-old female patient complains of depressed mood since break-up with boyfriend, 12 months ago. Has gained 10 kg, often sleeps for 12 h at night and has been markedly irritable. Occasional suicidal thoughts. Similar, but less severe reactions following romantic rejection in the past.

Case 3

A 55-year-old female patient with a 3-month history of severely depressed mood. Has lost 8 kg in weight, and wakes between 4 and 5 am. Unable to work due to poor concentration, and preoccupied with guilt over the break-up of her first marriage, 25 years earlier.

TABLE VII
Diagnosis assigned — Case 1

	(%)
Agoraphobia	22
Panic disorder/attack	17
Panic with agoraphobia	14
Anxiety neurosis	8
Anxiety	5
Panic state	4
Atypical depression	3

respondents giving drug therapy suggests that if behaviour therapy or psychotherapy is used by this group, it is likely to be in combination with drug treatment. Responses in respect of a treatment reflected those seen earlier in response to diagnostic cues, and again showed wide variation.

In Case 2, the range of diagnoses assigned indicates the least diagnostic agreement although most selected a diagnosis from the neurotic or atypical end of the depressive spectrum (Table IX); 25% assigned this as atypical depression.

For this case, 63% chose to use drug therapy. Treatment choices are shown in Table X, demonstrating a more decisive swing to TCAs/tetracyclics, than in Case 1. A significant percentage selected an MAOI (16%). Again , the UK, Spain, and Germany were the predominant prescribers of MAOIs but there was also a relatively large group of prescribers in Denmark (25%).

There was a further swing towards the MAOIs as second-choice therapy. There were no significant associations between diagnosis and treatment recommendations.

TABLE VIII
Case 1
Choice of treatment

	1st choice (%)	*2nd choice (%)*
TCA/tetracyclic	52	32
5-HT-reuptake inhibitor	7	11
MAOI	12	27
Benzodiazepine	30	20
Major tranquilliser	6	10
Other	7	6

TABLE IX
Diagnosis assigned — Case 2

	(%)
Reactive depression	35
Atypical depression	23
Depressive neurosis	16
Depression (unspecified)	5
Mixed reactive-endogenous depression	2
Personality disorder	2
Atypical and reactive depression	2

TABLE X
Case 2
Choice of treatment

	1st choice (%)	*2nd choice (%)*
TCA/tetracyclic	64	31
5-HT re-uptake inhibitor	14	24
MAOI	16	31
Benzodiazepine	10	8
Major tranquilliser	2	5
Other	3	6

In Case 3, a much broader agreement was seen, with 93% recommending drug therapy and TCAs/tetracyclics being the predominant choice (94%) and few cross-national differences. Similarly, diagnostic agreement was strong, with over 70% designating the diagnosis as endogenous depression.

Discussion

An important point in using a questionnaire method of survey is — how representative of the whole population are responses likely to be? The group at whom this questionnaire was aimed included all practising psychiatrists in Europe. Although there may clearly be a sampling error as a result of inaccuracies of mailing lists, in a sample of this size, this error is not likely to have a significant impact. However, the overall response rate was relatively low, and it was not possible to follow-up non-responders, but nevertheless, 1269 is still a considerable sample size.

The tendency to higher response rates from countries known to contain more relatively high prescribers of MAOIs suggests that the sample was probably biased towards MAOI prescribers, and although there was a significant percentage of responders who reported no current use of MAOIs, it is likely that the responders did preferentially represent relatively high prescribers. This sample may thus be a good representation of how MAOIs are being used by those who actually prescribe them.

The second problem is whether or not responses reflect actual clinical practice on the part of the respondent, rather than a theoretical answer. It does seem probable that treatment recommendations are likely to be based on personal experience. In addition, responses to stimulus material in the form of case vignettes paralleled the responses to earlier questions relating to diagnosis and treatment, and selection of treatment in general corresponded with responses to questions regarding frequency of prescribing. Thus, the data were internally consistent.

Given the shortcomings of the sample, some interesting findings have nevertheless been uncovered. It has confirmed that MAOI prescribing is still more common in those countries where psychiatrists have traditionally been viewed as high prescribers, for instance, in the UK, where the influence of Sargant and his colleagues has persisted.

There were also some interesting cross-country differences in respect of other psychotropics. Prescribing of TCAs was particularly high in Scandinavia, for example (probably reflecting the limited availability of other treatments), benzodiazepine prescribing across all diagnostic categories was high in Italy, while France, Belgium, and The Netherlands were using the highest percentage overall of 5-HT re-uptake inhibitors.

In depressive disorders, it appears that MAOIs are most commonly selected as drugs of first choice in either type of atypical depression cited in the study — whether related to anxiety or to reversed functional shift: 15% of all respondents selected MAOIs as first choice in atypical depression, and 28% as second choice. Prescribing of MAOIs in atypical depression was relatively higher in the UK, Ireland, Spain, and Germany.

The low use of MAOIs in endogenous depression is interesting in relation to the high number of respondents (60%) who felt that there was clear evidence in the literature to support the efficacy of MAOIs in this disorder.

Despite the evidence suggesting that the cheese reaction need not be a major problem with sensible dietary precautions (McGilchrist, 1975; Pare, 1985), the responses to the questionnaire suggest that it is still seen as a significant disadvantage for the older MAOIs. Interestingly, there was no difference in the rating of the cheese reaction as a significant disadvantage between high and low prescribers.

Many of the respondents indicated that the most important features of a new MAOI would be the reduction of reactions to tyramine in food, and adverse reactions to drugs. It is also noteworthy that other side-effects were not perceived as a problem, and it would be interesting to see how this would compare with the TCAs and tetracyclics. Given a new MAOI without a high propensity to the cheese reaction and to drug interactions, the large majority of this group indicated that they would extend their prescribing of MAOIs in both depressive and anxiety disorders.

With regard to anxiety disorders, there was lower agreement on choice of treatment amongst prescribers overall, particularly compared to the decisive treatment selection in, for example, endogenous depression. However, it must be noted that neither psychotherapy nor behaviour therapy was a fixed-choice option. Nevertheless, psychological and psychotherapeutic choices could be entered under the 'other' column, and they had in fact been selected in the depressive disorders.

A surprisingly high use of benzodiazepines was revealed by this study, particularly in anxiety neurosis, where it might be anticipated that treatment is often chronic and long-term. There were marked cross-national differences in this respect, the tendency to avoid them in the UK being noteworthy.

Overall, the study revealed a surprisingly low percentage of prescribers of MAOIs in anxiety, particularly in the light of recent studies in the USA, which have stimulated interest in the MAOIs in anxiety attacks (Buiges & Vallejo, 1987) and in social phobia. Given the increasing climate of opinion against benzodiazepines, an MAOI which is regarded as safer might change views greatly here.

The study findings indicate that overall, TCAs and similar drugs are still regarded as the first choice of treatment in a spectrum of depressive and anxiety disorders, if an antidepressant is to be used. They also suggest that a newer, safer MAOI might have a relatively broad spectrum of use, extending into endogenous depression, at least to judge by perceived efficacy.

It is also apparent from the study that in the last 30 years, only limited progress has been made in uncovering highly specific treatments or treatment indications in anxiety and depressive disorders. Specific treatment choices vary a good deal from one European country to another. What is more reassuring are the findings regarding diagnosis from the case vignettes. Thirty years ago, major differences between countries within Europe would have been probable. Now there is very considerable agreement, and the differences are minor, reflecting small ambiguities of the classification, rather than any real divergences of substance. These findings augur well for the future.

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The Genetics of Depression: Current Approaches

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It is widely accepted that depression shows a tendency to run in families. This is partly due to genetic influences — and the subject has been covered in recent reviews. This article, therefore, does not aim to recapitulate the genetic evidence but rather aims to elucidate the mode of transmission, to achieve an understanding of relevant gene-environment co-actions and interactions, and to describe attempts to identify and localise major genes.

That depression shows a tendency to run in families is a widely accepted and uncontroversial fact. There is good evidence that the tendency to familial clustering is partly due to genetic influences, and this has been the subject of a number of recent reviews (e.g. Reich *et al*, 1982; McGuffin & Katz, 1986, 1989). The purpose of this article, therefore, is not to recapitulate in detail the evidence in favour of a genetic contribution to depression, but rather to focus on recent studies which assume that the case for a genetic predisposition is proven. The main endeavours then are to elucidate the mode of transmission, to achieve an understanding of relevant gene-environment co-actions and interactions, and to identify and localise the major genes.

The evidence from genetic studies suggests that both genes and environment are important in the pathogenesis of depression. Environmental influences are probably most important in the less severe, more broadly defined depressive disorders, including those where a neurotic pattern of symptoms is found, but even in typical bipolar affective illness, the existence of discordant identical twins points to some degree of environmental determination. In Table I, data from recent twin studies are used to estimate the comparative contributions to the variance in liability to depression of genes (h^2), common family environment (c^2), and non-shared environment (s^2) i.e. those environmental influences which are specific to the individual and which do not impinge on his/her relatives. These calculations assume a multifactorial liability-threshold model, in which a variable termed 'liability to develop the disorder' is normally distributed in the population, such that only those individuals whose liability at some stage exceeds a certain threshold manifest the disorder (Falconer, 1965; Reich *et al*, 1972). These estimates have large standard errors because the sample sizes, although currently the best available, are fairly small (McGuffin & Katz, 1986, 1989). Nevertheless, the evidence provides a strong impression that Kraepelinian-type manic-depressive illness, as studied by Bertelsen *et al* (1977), is a predominantly genetic condition, while neurotic depression is mainly of environmental origin and clusters in families because of common family environmental effects (Torgersen, 1986). Major affective disorder, as judged from the preliminary results of a recent Maudsley Hospital Register-based study (McGuffin & Katz, 1989), appears to occupy an intermediate position. We view the intermediate position of major affective disorder as scarcely surprising, since clinical experience suggests that the DSM–III or DSM–III-R category (American Psychiatric Association, 1980, 1987) is a mixture of what in Britain would be classified as either ICD–9 manic-depressive illness (296) or depressive neurosis (300.4).

It is important to stress that concepts such as heritability have serious limitations, and that estimations of h^2 and c^2 should not be seen as ends in themselves. Nevertheless, the results summarised in Table I provide more than a hint that if our aim is to search for major genes, we should concentrate on the more severe forms of manic-depressive disorder, while if our main aim is to investigate the interplay between genes and environment, we should probably focus on the more broadly defined milder forms of depression.

The search for major genes for severe affective disorders

When dealing with a trait which does not lend itself to a clear all-or-none dichotomy, or where typical Mendelian segregation patterns are not observed, three complementary strategies can be used to detect major gene effects.

The first is to analyse the distribution of the trait in the population. If some continuous measure can be applied and a mixture of two or more distributions can be demonstrated, then this can be taken as suggestive evidence of a major gene (particularly if there are three distributions in the proportions predicted by the Hardy–Weinberg Law). This approach has been successfully used for traits such as platelet monoamine oxidase activity, which are of potential psychiatric interest (Rice *et al*, 1982). Unfortunately, there is as yet no satisfactory continuous trait measure which is strongly associated with liability to become depressed and is not

TABLE I
Contributions to the variance in liability to depression: calculations based on recent twin studies

	h^2 *(Additive genetic)*	c^2 *(Common environment)*	s^2 *(Non-shared environment)*	*Kp (%) (Population risk)*
Manic depressive illness (Bertelsen *et al*, 1977)	0.86	0.07	0.07	3.0
Major affective disorder (McGuffin & Katz preliminary data)	0.52	0.30	0.18	4.7
Neurotic depression (Torgersen, 1986)	0.08	0.54	0.38	6.0

confounded by depressive states (Katz & McGuffin, 1987). The second strategy is to carry out complex segregation analysis based on the distribution of the trait within pedigrees, e.g. applying the mixed model of Morton & MacLean (1974). This approach is applicable either to continuously measured traits or to present/absent characters, and can therefore be used in the analysis of manic-depression, as can a third strategy, which is to search for linkage between a putative manic-depression gene and genetic markers.

There has been a small number of studies using modern methods of segregation analysis in manic-depressive illness. Bucher *et al* (1981) have applied to combined data from a set of families ascertained through bipolar probands, a model based on the concept of transmission probabilities (Elston & Yelverton, 1975). Here, it is considered that there is a major locus with two alleles, A_1 and A_2, where A_2 is the mutant or diseased allele. The probabilities of parents transmitting the A_2 allele to their offspring are 0, 0.5 and 1, for parents of the type A_1A_1, A_1A_2, and A_2A_2 respectively. It is then possible to test the alternative hypotheses of: (a) no transmission (when the transmission probabilities all approximate to 0); (b) Mendelian transmission (when the probabilities are 0, 0.5 and 1); or (c) some other form of vertical transmission which is non-Mendelian (where the transmission probabilities exceed 0 but deviate from Mendelian expectations). Bucher *et al* (1981) concluded that the last of these hypotheses, i.e. vertical transmission not mediated via a major locus, best explained the data. Subsequently, O'Rourke *et al* (1983) performed a segregation analysis applying the 'combined' model of Reich *et al* (1982), which is similar conceptually to Morton & MacLean's (1974) mixed model. Here, it is assumed that liability to develop the disorder is made up of a combination of a major gene effect, a familial multifactorial effect (polygenes plus common family environment), and a residual environmental component. The procedure is to test a full mixed model against reduced models which form its subsets, and a computer program is used to arrive at an iterative solution which provides the best fit for each model. This occurs when the likelihood that the hypothesis is correct, given the observed data, is maximised. Hypotheses can then be compared directly, using a likelihood ratio test which depends on the fact that twice the difference in the log likelihoods approximates asymptotically to a χ^2 distribution. O'Rourke *et al* (1983) were able to show that the combined model was superior to a multifactorial one, since there was a substantial and significant difference in the log likelihoods. The likelihood ratio χ^2 was however not significant for the difference between the combined and the major gene model, and the authors were therefore able to conclude in favour of the major gene hypothesis.

Similarly, an even larger sample of families analysed by Rice *et al* (1987), using a mixed model approach, gave evidence for the presence of a major locus, when controlling for the effects of birth cohort and age of onset. However, Rice *et al* then applied a unified model (Lalouel *et al*, 1983), which effectively amalgamates the concepts of the mixed model and of transmission probabilities. It was found that the evidence for a major gene was less convincing when the mixed model was compared with the more general vertical transmission model: i.e. that when the probabilities of transmission of the major gene were not constrained to Mendelian values, the likelihood increased significantly.

Linkage studies can potentially provide more convincing evidence of the existence of a major gene. The underlying notion is a simple one: the co-segregation of the disease and a genetic marker is studied within pedigrees containing multiple affected individuals. A tendency within pedigrees for a particular allele to be consistently associated with the disease, i.e.

showing a departure from Mendelian independent assortment, suggests that the disease gene and the marker genes occupy loci in close proximity on the same chromosome. In practice, however, performing linkage studies is not so simple. One important difficulty is that standard methods of linkage analysis using the lod score method (Morton, 1955) assume that the mode of inheritance of the disease trait is known. As discussed above, this is not so for manic-depressive illness. Although there are suggestions of major gene inheritance, this can only exist if we allow that there is incomplete penetrance (i.e. the probability that the trait is expressed given the genotype is less than 1). Although this is not an insuperable problem, it does create difficulties for statistical analysis (Sturt & McGuffin, 1985).

Despite this, exciting possibilities have been opened up by the arrival of the new genetics of recombinant DNA. Until comparatively recently, would-be investigators had only a limited number of genetic markers with which to work. These included red cell types, histocompatibility antigens (HLA types), blood cell enzymes, chromosome banding polymorphisms, and various protein polymorphisms in the blood. These are now referred to as 'classical' markers, and even with good collaboration between laboratories, it is rarely feasible to study more than about 25–30 loci. This leaves, at a conservative estimate, about 80% of the human gene map uncovered, and it has been known for some time that the number of markers required to span the entire genome is about ten times as great (Lange & Boehnke, 1982).

Recombinant DNA technology has now produced an entirely new generation of markers – restriction fragment length polymorphisms (RFLP) – which exist because of individual differences in the sequence of bases in the DNA molecule. Bacterial enzymes – 'restriction endonucleases' – recognise and cut DNA at specific sites, producing fragments which differ in length between different individuals. Particular fragments can be detected using radio-labelled complementary DNA (cDNA) probes in the technique of 'Southern blotting' (Southern, 1975). Such RFLPs segregate as simple Mendelian co-dominants, and a sufficient number are now available to perform a complete human genetic linkage map (Donis-Keller *et al*, 1987).

The most provocative findings to date concern the H-ras locus on the short arm of chromosome 11, since there is strong evidence in a large North American pedigree of linkage between this locus and a gene for bipolar disorder (Egeland *et al*, 1987). Unfortunately, other investigators have not only failed to confirm such a linkage, but have effectively excluded it in other North American, Icelandic, and Irish pedigrees (Detera-Wadleigh *et al*, 1987; Hodgkinson *et al*, 1987; Gill *et al*, 1988). Since the evidence for linkage was strong in this one positive study, the combined findings raise the possibility that there is heterogeneity within bipolar disorder so that some forms are linked and others not linked to the H-ras locus. On performing the heterogeneity test of Morton (1956), there is indeed highly significant evidence of heterogeneity, which will enable us to reject the null hypothesis of homogeneity within bipolar disorder (i.e. with the spurious 'chance' positive appearance of linkage in one pedigree and not in others). The positive North American study derived from an investigation of the Old Order Amish (Egeland *et al*, 1987) – a religious sect in the State of Pennsylvania, which effectively forms a genetic isolate. It therefore needs to be established whether these chromosome 11 linkage results have a wider application, which can be replicated in other populations.

Against this background of speculation on genetic heterogeneity, there has been a rekindling of interest in the possibility that some forms of affective illness are transmitted by X-linked genes. The first detailed descriptions of pedigrees which appeared to be X-linked, based on the co-segregation of affective illness and colour blindness, were published 20 years ago (Reich *et al*, 1969). It has since been demonstrated that many families show father-to-son transmission, which effectively excluded X-linkage, and various groups have failed to confirm linkage with X-chromosome markers (Gershon *et al*, 1980). Hence, X-linkage can at best account for only a minority of inherited forms of affective illness. Nevertheless, there have been two recent reports of family linkage studies where the probability of X-linkage is high. Baron *et al* (1987) reported X-linkage between X-chromosome markers and manic depression in Israeli families, while in Belgium, Mendelwicz *et al* (1987) produced evidence of linkage with an X-chromosome polymorphic DNA marker.

Although the recent X-linkage and chromosome 11 results are provocative, it seems that the majority of cases of manic-depressive illness cannot be accounted for by either of these forms of transmission. Both sets of results now need to be replicated in independent centres, but of equal immediate relevance and greater longer-term importance will be the search, carried out systematically through the human genetic linkage map, for other loci linked to major genes for manic depression.

Genes, environment and depression

The second major area of current interest which will be discussed here explores further the complex path between abnormal genes and abnormal emotional states. Although most researchers will concede that distress and adversity, in addition to genes, play a role in the aetiology of depression, it is only quite recently that attempts have been made to study familial predisposition and adversity at the same time. A pioneer study was that of Pollitt (1972), who divided a series of depressed probands into two groups — those whose illness followed some form of physical or psychological stress, and those where there was no obvious environmental cause. Among the relatives of probands whose illness followed some form of stress, the morbidity risk of depression was 6–12%, but among the relatives of probands who had no obvious precipitant for their depression, the morbidity risk rose to 21%.

Over the past two decades, there have been serious attempts by socially orientated researchers to objectify measures of stress and to overcome the formidable methodological problems in quantifying adversity. As a result, methods for identifying and evaluating life events are well established, and there is good agreement that events which carry a high contextual threat or which are associated with 'exits' (e.g. bereavement, divorce) are commoner in depressed subjects, prior to the onset of their disorder, than in healthy controls. Regrettably, just as geneticists have often regarded environmental factors as residual sources of variation, so too life-event researchers have paid little heed to the effects of genes. In view of this, workers at the UK Medical Research Council Social Psychiatry Unit and the Genetics Section of the Institute of Psychiatry, London, embarked on a collaborative family study of depression. The remainder of this paper will focus on this work in an attempt to answer three questions:

(a) Is the pattern of symptoms of endogenous or neurotic depression related to absence or presence of stress?
(b) Is there an inverse relationship between familiality/genetic loading and 'reactivity'?
(c) Do stress-related and non-stress-related forms of depression 'breed true'?

The endogenous/neurotic dichotomy

This sample of patients has been described in detail elsewhere (Bebbington & McGuffin, 1989). The probands consisted of a consecutive series of patients presenting to the Bethlem Royal and Maudsley Hospital, London with a recent well-defined onset of depression, who fulfilled clinical criteria after interview using the Present State Examination (PSE) (Wing *et al*, 1974) and who lived within the boundaries of the old London Borough of Camberwell. The other main sampling constraints were the attempts to obtain both approximately equal numbers of men and women and equal numbers of patients in the endogenous and neurotic categories respectively. The controls were subjects from the same catchment area, investigated in the earlier Camberwell Community Study of Bebbington *et al* (1981). Both the community sample and the family sample were studied using the PSE and the Life Events and Difficulties Schedule (LEDS) (Brown & Harris, 1978). A total of 130 patients (76 women, 54 men) were studied, and personal interviews were carried out by separate investigators on first-degree relatives of 83 patients.

An endogenous group of cases was defined as those falling within the CATEGO classes D and R — depressive psychosis and retarded depression — while a neurotic group was defined as those conforming to classes N and A — depressive neurosis and anxiety/depression (Wing *et al*, 1974). Previous research which focuses on the pattern of symptoms of depression and on the presence or absence of preceding adversity is difficult to interpret. Multivariate statistical studies (e.g. Paykel, 1971) have almost all found that absence of adversity discriminates endogenous from reactive cases as efficiently as any endogenous symptoms (for review, see Bebbington & McGuffin, 1989). Although absence of adversity was significantly associated with endogenous symptoms, this appeared mainly to be accounted for by the effects of age (Paykel, 1971). Thus, depression in older patients is more likely to be of an endogenous pattern and life events are less common in older subjects.

By contrast to multivariate statistical studies, investigations specifically examining the association between the pattern of symptoms and adversity have resulted in a very mixed picture. Some recent studies do provide support for an association between adversity and a neurotic depressive profile (e.g. Paykel *et al*, 1984; Roy *et al*, 1985), but this is not a consistent finding. Even without controlling for age, the experience of preceding adversity was similar in endogenous and reactive groups, in recent reports by various authors (e.g. Katschnig *et al*, 1981; Brugha & Conroy, 1985; see also Bebbington & McGuffin, 1989 for review).

Data from the Camberwell Collaborative Study are summarised in Table II. Events categorised as of severe or moderate threat and which are independent or possibly independent of the subject's behaviour and mood state (Brown & Harris, 1978) are commoner in depressed men than in depressed women, and markedly more frequent in all depressed subjects in the 3-month period prior to the onset of depression than in community controls. However, there is no evidence of any difference in the frequency of life events, when the endogenous and neurotic groups are compared.

Numerous previous studies have shown only slight differences in the expected direction (i.e. events more often associated with neurotic depression), and there is

TABLE II
Prevalence of life events during the 3 months prior to onset of depression compared with 3-month prevalence in controls

	Depressed patients		*Controls*
	Neurotic (%)	*Endogenous (%)*	*(%)*
Men	31	27	7
Women	41	45	11

therefore a need to beware of the possibility of committing a type 2 error. This sample was designed to be large enough to detect a genuine difference of 25% between the two groups at the 5% level of significance, with 90% power; one can therefore be reasonably confident that there really exists no difference.

The findings are in marked contrast to the earlier results of Bebbington *et al* (1981), which showed a clear association between threatening life events and the onset of neurotic depression, but little association in subjects with an endogenous pattern of symptoms. For the present, it is therefore an open question as to whether these discrepant findings relate in some way to the different characteristics of the two samples, i.e. the differences between subjects from a community sample identified as 'cases', and subjects who are actually patients of a psychiatric hospital.

Familiality and reactivity

Much of the earlier literature mentioned above hints that depression which follows unpleasant events is less likely to be associated with a family history of the same disorder than depression which appears to arise spontaneously and without obvious precipitants. As mentioned above, the only previous attempt to test this directly was that of Pollitt (1972), whose findings were clearly in the expected direction. However, the findings of our present study are rather different (Table III): of 83 probands whose families were studied, 30 had an onset of depression associated with a 'severe' event. Following the terminology of Brown & Harris (1978), severe events were defined as those which are independent or possibly independent, with a threat rating of 1 (marked) on a 4-point scale or a rating of 2 (moderate) where the event is self-focused. It is possible to take different cut-offs for defining 'life-time ever' depression in first-degree relatives, and to present both life-time prevalence and morbid risk (Table III). But no matter which figure is chosen, there is no statistically significant difference in the frequency of depression between the relatives of probands whose onset was event-associated and relatives of probands who suffered no detectable severe events in the three months prior to the onset of illness. Indeed, using the broader definition of depression in relatives, there was a trend in the opposite of the predicted direction; i.e. the life-time prevalence and morbid risk of depression was higher in the relatives of probands who had depression associated with life events.

Some forms of adversity are more long-term than discrete events, and these are categorised by Brown & Harris (1978) as 'chronic difficulties'. 'Serious chronic difficulties' are those which warrant a threat rating of 1, 2 or 3 on a 6-point scale. Table IV presents the life-time prevalences of moderate plus severe depression in first-degree relatives, according to whether the probands' onset of depression was associated with life events or chronic difficulties. Considering this broader range of adversity, the highest life-time prevalence of treated depression is found among the relatives of probands who have encountered both categories. However, a logistic regression analysis, with 'life-time ever' affected status of relatives as the response variable and the presence or absence of life events and chronic difficulties in the proband as predictor variables, established no significant effects.

These findings cannot be regarded as completely

TABLE III
Proband type and the frequency of depression in first-degree relatives (adapted from McGuffin et al, 1988)

Probands		*First-degree relatives*				
			Moderate and severe depression		*Severe depression*	
Onset of depression	*No.*	*No.*	*LP (%)*[1]	*MR (%)*[2]	*LP (%)*[1]	*MR (%)*[2]
Associated with life event	30	112	20.5	33.7	6.3	11.3
Not associated with life event	53	203	12.8	20.1	7.4	12.2

1. LP = lifetime prevalence.
2. MR = morbidity risk to age 65 using a modified Strömgren method of calculation.

TABLE IV

Adversity in probands and the lifetime prevalence (LP) of moderate plus severe depression in first-degree relatives

Proband			*First-degree relative*	
Onset associated with:				
Life events[1]	*Chronic difficulties*[2]	*No.*	*No.*	*LP (%)*
Yes	No	17	69	17
No	Yes	17	64	11
Yes	Yes	10	43	26
No	No	39	139	14
		Total	315	

1. Defined as in Table 1.
2. Independent and possibly independent chronic difficulties with a threat rating of 1, 2 or 3 (Brown & Harris, 1978).

contradictory to those of Pollitt (1972), since the majority of precipitants of disorder in Pollitt's 'justifiable' group of depressed probands consisted of infections or other physical stressors, whereas in our series, none of the 83 probands appeared to have important physical factors contributing to the onset of their depression. This may again have something to do with different settings. Pollitt's study was carried out in the psychiatric department of a general hospital, whilst ours was performed in a specialist postgraduate psychiatric teaching hospital, where depression secondary to physical illness is less common. Nevertheless, our results do present a serious challenge to the practice of dividing depression into a non-familial-reactive category and a familial non-reactive category. Again, this corresponds to our failure to demonstrate a difference in the association of life events with the onset of endogenous and neurotic patterns respectively of depression.

TABLE V

Current psychiatric disorder and recent life events in first-degree relatives of depressed probands (adapted from McGuffin et al, 1988)

Onset of depression in probands	*Relatives with recent life events*[1]		*Relatives with no recent life events*[1]	
	No.	*Cases*[2] *(%)*	*No.*	*Cases*[2] *(%)*
Associated with life event	41	12.2	58	15.6
Not associated with life event	61	26.2	84	14.3

1. Life events defined as all events which were independent or possibly independent and had threat rating of 1 or 2, irrespective of focus; recent life events in relatives as events in 3 months prior to onset of depression or prior to interview if relative is well.
2. Current ID level of 5 or greater.

The familiality of depression and of adversity

In the light of the results just described, a positive answer should probably not be expected to the third question posed at the outset of this study. We should not expect to find that there is homotypia – a tendency for event-related and non-event-related depression to 'breed true' within families. Indeed, no such homotypia was found. Table V summarises data on a subset of 244 relatives who were personally interviewed using both the PSE and the LEDS, consideration being restricted to current illness. Forty-two first-degree relatives (17.2%) could be defined as current 'cases' of depression, and a substantial proportion of these (45%) had had previous episodes. For two subjects, the present onset had been insidious and difficult to disentangle from previous episodes, but for the remainder, probable onsets of significant depressive symptoms had occurred within the 12 months prior to interview.

Therefore, for subjects who were currently depressed, it was possible to consider the 3-month period prior to onset, when classifying the depression as event-associated or not. It is apparent from the table that there is no tendency for life event-associated depression in probands to indicate an especial risk of similar depression in their relatives. This was more formally tested using a logistic regression model, with current illness in relatives as a response variable and life events in relatives and in probands as the predictors. Neither the predictors nor the interaction proved to be significant. It is also noteworthy that in the first-degree relative sample, the association between recent life events and current illness appears to be small.

To examine this effect and the relationship between familiality of depression and of life events in greater detail, the personally interviewed first-degree relatives were compared with the representative community sample of Bebbington *et al* (1981) where, as mentioned above, the data were collected using virtually identical methods of assessment. The main results of this comparison are summarised in Table VI. Three main findings emerged. Firstly, current cases were significantly more frequent among the first-degree relatives than in the community. This is perhaps scarcely surprising, in view of earlier comments in reviewing the literature that depression is nearly always more frequent in relatives of depressed patients than in the general population. However, most family studies have taken a fairly narrow definition of depression over a lifetime, whereas here, a rather broader definition is used and current illness is considered.

Secondly, the association between recent life events and current disorder in the community sample is marked and striking, whereas in the first-degree relative sample, it is weak. In order to test whether there was a more general association between current illness and adversity in relatives, a further analysis was performed which included chronic difficulties. However, the adversity/illness association remained weak: 23 of 121 relatives experiencing adversity were current cases, compared with 19 of 123 with no adversity.

The third main finding was that not only does current illness appear to cluster in families, but so do recent life events. The increased rate of life events among first-degree relatives, compared with the community sample, was highly significant and remained so even when all potentially confounding proband-related events were removed. When life events over time were plotted in the relatives' sample, no close temporal proximity between the peak of relatives' life events and the probands' onset of illness was obtained. Therefore, it seemed unlikely that the high rate of events was associated with the turmoil created by the onset of the probands' disorder or by certain life events which impinge both upon the proband and on other family members. Performing a logistic regression analysis and taking current depression as a response variable, both the experience of life events and being a first-degree relative of a depressed proband were found to have significant effects, but there was also a highly significant life-event-by-relative interaction. This is because, as pointed out above, the effect of recent life events on current illness was large in the general population, but small in the first-degree relatives of depressed probands.

Discussion

Given their consistency, it is not surprising that the results of genetic studies are widely accepted as providing a firm foundation for the notion that there is a biological basis to depression. The area of greatest topical interest, and the one which holds greatest promise of major advances, concerns the study of severe forms of affective illness, principally bipolar disorder, where genes account for as much as 80% of the variance in liability. Statistical studies have provided suggestions of major gene effects here, and although it is so far unreplicated, the report of linkage between a gene for manic-depressive illness and a DNA marker on chromosome 11, together with the renewal of interest in the possibility of X-linkage in some forms of disorder, has induced a mood of excitement among researchers. In order for expectations to be fulfilled, both chromosome 11 and X-linkage findings need to be well replicated in independent centres, and there must be systematic and concerted search for other major loci. This is because the results so far are strongly suggestive of genetic heterogeneity in manic-depressive illness, but they also suggest that most forms are not transmitted via either chromosome 11-linked or X-linked genes.

Of less dramatic impact, but also of less high risk of producing hit-or-miss results, are studies which attempt to examine environmental and family-genetic factors

TABLE VI

Current depression and recent life events in first-degree relatives of depressed probands compared with a community sample (adapted from McGuffin et al, 1988)

	Subjects with recent life events		*Cases among subjects with recent life events*		*Cases among subjects with no recent life events*		*Total cases*	
	No.	*(%)*	*No.*	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Community sample ($n=289$)	21	(7.3)	12/21	(57.1)	20/268	(7.5)	32	(11.1)
First-degree relatives ($n=244$)	70	(28.7)	15/70	(21.4)	27/174	(15.5)	42	(17.2)

simultaneously. This area has difficulties in definition of a phenotype, since it necessarily focuses on unipolar disorder, which is broadly defined and presents classificatory problems for researcher and clinician alike (Kendell, 1976; Farmer & McGuffin, 1989). Nevertheless, the Camberwell Collaborative Depression Study has produced a number of unexpected and thought-provoking findings.

Perhaps least unexpected among these was the finding that adversity in a hospital-based sample is no more closely associated with a neurotic pattern of depressive symptoms than with an endogenous one. More unexpected, given the results of previous studies, was the finding that depression was as common among the relatives of probands whose illness followed stress as among those of probands whose illness was not in any discernible way reactive. Together, these results provide strong evidence against the acceptance of earlier classifications of depression into 'endogenous' and 'neurotic-reactive' subtypes, and no indication has been found that such subtypes 'breed true' within families.

The most surprising finding was that not only is depression familial, but so also is the tendency to encounter (or to report encountering) threatening life events. Furthermore, within families, exposure to life events showed only a weak and non-significant association with depression. This suggests that life-event-associated depression is something which occurs in hazard-prone, rather than in simply stress-susceptible individuals. Indeed, it is a possibility that part of the association between life events and depression which has been consistently shown in population studies is due to the fact that both reflect a common familial origin. However, it should be noted that the evidence so far derives from a family study, which cannot satisfactorily distinguish between traits which are familial because of the shared environment and those which are largely a result of genes. It is tempting to speculate that the most salient personality factor involved in the familial association between life events and depression is related to cognitive style. It may be that a certain cognitive set is associated with the perception of events as threatening, the retention of such events in the memory, and the tendency to develop depressive responses. Further exploration of this proposition will require the analysis of cognitive measures on family data and on a separate sample of monozygotic and dizygotic twins; both of these are currently in progress.

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Suicide and Antidepressant Overdosage in General Practice

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Depression is a very common condition, and most depressed patients in many countries are treated by their General Practitioners. It is a frequent cause of suicide – one of the major causes of death in young adults – and is the disorder most commonly associated with deliberate self-poisoning, a large percentage of suicides being due to poisoning with drugs that are only available on prescription. Self-poisoning with older tricyclic antidepressants (TCAs) poses major clinical management problems, since the majority of patients who overdose with these agents do not reach hospital alive. Though there is no convincing evidence that any one antidepressant is more effective than others or more rapid in onset of therapeutic action, antidepressants do differ substantially in their side-effect profiles and in their toxicity in overdosage, those introduced before 1970 being relatively more toxic. Since suicide rates have been reduced by limiting the availability of toxic substances such as barbiturates and harmful domestic gas, restricting the use of older antidepressants in favour of newer, safer compounds for depressed patients being treated in general practice would also seem to be advisable.

In the UK and many other countries, the great majority of depressives who receive treatment do so from General Practitioners (GPs): depression is one of the commonest diagnoses made in primary care settings. Clinical trials have convincingly shown that antidepressant drugs are therapeutically effective, and when administered in an adequate dose for a sufficient duration, they form the cornerstone of treatment.

Many antidepressants have been developed since the introduction of the tricyclic compounds (TCAs) and monoamine oxidase inhibitors (MAOIs) between the late 1950s and early 1960s – some of them chemically similar to the originals, and others very different. Although not differing significantly in overall efficacy or speed of action, they do vary substantially in two very important respects – side-effect profiles and toxicity in overdosage. Thus, consideration of the nature of unwanted effects and possible adverse reactions is important in determining the choice of a suitable antidepressant for a particular patient.

Suicidal ideation is a common feature of major depressive disorder, and depression a frequent cause of successful suicide or suicidal behaviour. During some periods of life, suicide is one of the most important causes of mortality, surpassed only by accidents – especially road traffic accidents – and cancer. There is evidence that many individuals who attempt or successfully commit suicide have had recent contact with medical services, particularly GPs, while a common method of self-destruction is by taking psychotropic medication that had been properly prescribed.

Taken in overdose, some antidepressants cause serious cardiological and neurological disturbances which can pose major clinical problems in resuscitation. Relating reported deaths to the numbers of patients treated or to the number of prescriptions issued by GPs in the UK has shown that older antidepressants (i.e. introduced before 1970) are generally more toxic in overdosage than those which have become available more recently – although there are some individual differences between drugs. Toxicity in overdosage should therefore be an important consideration in the choice of a suitable antidepressant. Because of the known risk of antidepressants in overdosage, depressed people who are seen as out-patients or in primary care should preferably be treated with those that have relatively low toxicity.

Epidemiological aspects

There is now a substantial body of evidence which suggests that depression is a major contributor to the high level of psychiatric morbidity in the community. The analysis by Goldberg & Huxley (1980) reported a prevalence of 250 per thousand persons at risk for all forms and of 140 per thousand for conspicuous psychiatric morbidity, as diagnosed by GPs. In the USA, Blazer *et al* (1988) stated that "depending upon the cut-off point employed", between 13% and 20% of the population have significant depressive symptoms. They noted, however, that using DSM–III criteria, analyses of data from four sites in the Epidemiologic Catchment Area (NIMH–ECA) programme, sponsored by the National Institute of Mental Health, indicated a prevalence of diagnosed major depressive disorder of 1.9% to 3.5%, together with a non-concurrent prevalence of dysthymia (depressive neurosis) of 2.1% to 3.8%, and of bereavement reactions of 0.1% to 0.3%. Thus, the results of these surveys suggest that at any time, between 3% and 8% of the population can be classified into existing DSM–III diagnoses for depression.

Clearly, these data suggest a discrepancy between the prevalence of depressive symptoms (13–20%) and that of depressive disorders (3–8%). This discrepancy may be explained by the existence of syndromes in the community which are not described by DSM–III. The study by Blazer *et al*, for example, identified five profiles in a community population: one included a set of symptoms nearly identical with those associated with the DSM–III classification of major depression, but other depressive syndromes emerged, including a premenstrual one among younger women, and a mixed anxiety–depression syndrome. DSM–III does not recognise the existence of such a syndrome as this last one, although the results of a number of clinical studies have suggested its existence. Prusoff & Klerman (1974), for example, reported that 40% of a neurotic out-patient group showed mixed anxiety–depression, and could not be classified into either diagnostic category alone.

The results of one UK community survey (Dunn & Skuse, 1981) have revealed that three-quarters of all women and over half of men visit their GP at least once in 20 years with a psychiatric complaint. Approximately 70% of these women and 34% of the men have an episode of depression. Surveys in general practice consistently report that depression is responsible for 10–20% of consultations, and that it is the fourth to thirteenth most frequent diagnosis made by a GP.

Goldberg & Bridges (1987) reported that in 590 patients presenting in general practice with a "new complaint", 15.8% fulfilled the diagnostic criteria for generalised anxiety disorder, 12.7% those for major depressive disorder, and 3.1% those for dysthymic disorder. Of the 195 psychiatric cases identified, 47.8% could be regarded as generalised anxiety disorder, 38.4% as major depressive disorder, and 9.3% as dysthymic disorder. These and many other data suggest that depression is a very common disorder, which is frequently seen and treated by GPs.

Depression, suicide and deliberate self-harm

Depression is the disorder most commonly associated with deliberate self-harm (DSH) (Weissmann, 1974; Newsom-Smith & Hirsch, 1979; Urwin & Gibbons, 1979). Barraclough *et al* (1974) found diagnosable psychiatric illness in 93% of cases of suicide – uncomplicated depressive illness in 64%, alcoholism in 15%, and schizophrenia in 3%. The importance of psychiatric illness in DSH is more contentious, though: Morgan *et al* (1975) estimated that up to 12% of those who commit DSH suffer from psychotic mental illness and that 39% of the men and 59% of the women are likely to have reactive depression. A report of the Edinburgh Regional Poisons Treatment Centre (Report, 1978), however, showed that depressive illness or depressive reaction could be identified in only 11% of males and 18% of female admissions for DSH.

Robins *et al* (1959) found that about two-thirds of individuals who successfully committed suicide had visited their family doctor in the previous week. In another study (Barraclough *et al*, 1974), it was found that more than 90% of the cases had consulted either a family doctor or a psychiatrist within 1 year of death, and that 48% had done so within 1 week. In fact, 24% received psychiatric help in the 12 months preceding death, and half of these had made contact in the final week. More than 80% of the suicides studied were receiving psychotropic drugs, which implies that they had been recognised by their doctors as being psychologically disturbed.

Over the past four decades there have been substantial changes in Britain in the numbers of suicide by method. By 1980, poisoning by either solid or liquid substances accounted for 54% of female and 25% of male suicides (Bulusu & Alderson, 1984); taking male and female suicides together, it was the most common means of completed suicide. A report from the Samaritans (Information Sheets), covering the period 1975 to 1987 in England, Scotland, and Wales, indicated that hanging was the major method in men, accounting for 28% of cases, and that poisoning is responsible for the largest number in women – 26%. Taking both sexes together, the following percentages were seen for the various methods used – hanging, strangulation and suffocation 30%; poisoning by solid or liquid substances 25%; poisoning by gases 22%; drowning 5%; use of firearms and explosives 5%; jumping from a high place 4%; and using cutting or piercing instruments 3%. However, overdose was the most common method used in DSH.

In a large percentage of suicides due to poisoning with drugs, the medicines employed are available only on prescription. However, the drugs used by a particular person in an episode of self-poisoning may not have been prescribed for his/her use: Jones (1977) found that one-third of his sample had taken an overdose of a medicine which had been prescribed for a friend or a relative. In a significant proportion of episodes of DSH, drugs which are readily obtained without prescriptions, e.g. aspirin and paracetamol, are used.

Suicide rates

In 1987, there were 3983 deaths in England and Wales as a result of suicide and DSH (Office of Population Censuses and Surveys, 1988). Accidents and violence together were responsible for 17 818, of which 11 522 were accounted for by accidents and adverse events and 148 by homicide. However, there were 2149 deaths in which the cause was undetermined, and it is likely that some of these may have been due to suicide. It has been suggested therefore (e.g. by The Samaritans), that the true number of deaths from suicide was in excess of 4500. In the January to March quarter of 1988, there were 4889 deaths from accidents and violence: 1210

TABLE I

Death rates per 100 000 of population and the actual numbers of death for a selection of countries in 1988

	Death rates per 100 000		*Number of deaths*	
	M	*F*	*M*	*F*
Austria	40.1	15.7	1445	624
Belgium	30.9	14.1	1488	714
Denmark	35.6	19.9	899	517
France	32.9	12.9	8872	3657
Germany (Fed)	26.7	11.8	7836	3763
Hungary	65.9	25.6	3377	1405
Ireland	12.2	3.4	216	60
Italy	11.3	4.5	3123	1331
Netherlands	13.9	8.2	988	606
Portugal	14.3	4.7	709	251
Sweden	27.1	10.1	1119	430
Switzerland	35.0	13.7	1118	458
UK	11.8	4.6	3263	1331
USA	19.9	5.1	23 145	6308

TABLE II

Causes of death in 1987 in age groups 15–24 and 25–34 in England and Wales

	15–24		*25–34*	
	M	*F*	*M*	*F*
Suicide and self-injury	461	105	618	168
All accidents	1763	378	1056	274
Motor vehicle accidents	1338	303	624	161
Malignant neoplasms	305	185	535	652

due to motor vehicle accidents, 1224 to accidents in the home and in residential institutions, and 1116 to suicide.

However, suicide rates vary by country and by age. The overall death rates per 100 000 of the population and the actual numbers of death for a selection of countries in 1988 are shown in Table I. The highest rates are seen in the elderly: the rate in the UK for 75- to 84-year-olds, for example, is 142 per million, compared with a national rate of approximately 100 per million, but it is in the young that suicide emerges as a major cause of death. In England and Wales in 1987, suicide was second only to motor vehicle accidents as a cause of death in 15- to 24-year-olds, and was only surpassed by accidents and malignant neoplasms in those aged 25 to 43 (Table II).

Effects of antidepressant overdosage

Tricyclic antidepressant overdose presents a typical and serious picture, which includes coma, seizures, hypertension, abnormalities of the electrocardiogram, and a variety of arrhythmias. Patients who have overdosed with TCAs require very intensive care, but in spite of this, the outcome is often fatal. It is, however, not generally realised that 70–80% of individuals who take TCA overdoses do not reach hospital alive. In the case of the older MAOIs, large doses produce hypomania and euphoria, followed by coma, with hypotension or acute hypertension, and sometimes sub-arachnoid haemorrhage.

Of the newer 'tricyclic' compounds, maprotiline appears to be pharmacologically and toxicologically similar to its conventional forbears, whereas the information so far available suggests that lofepramine is much less toxic. Overdoses of both mianserin and trazodone may cause drowsiness, but neither is associated with convulsions or ECG abnormalities. While data on overdosage with serotonin (5-HT) re-uptake inhibitors such as fluoxetine and fluvoxamine are limited, experience so far suggests that these agents lack the severe toxicity of the TCAs.

Experience with the new reversible MAOI, moclobemide is also limited, but observations on six depressed patients who tried to commit suicide by ingestion of an overdose of this drug, alone or in combination with others, suggest that it is safe, even in significant overdose (Hetzel, unpublished data, Hoffmann-La Roche). In these cases, drowsiness was the principal effect; there were no convulsions, important cardiotoxicity, respiratory failure, or other life-threatening complications after doses of up to 2g.

An important consideration is the cost of caring for overdose patients, though it is difficult to obtain information on this, either in suicide or DSH. However, it was estimated that in the UK in 1977, 92 000 adult admissions cost £15–£20 million, or £200 per case. Such costs would now be considerably greater and, of course, the cost of the intensive care of a patient with a TCA overdose would be substantially greater than the average figure per case.

Toxicity of antidepressants

Since the introduction of antidepressants, as we understand the term at present, in the late 1950s, there have been four main considerations in their use — overall efficacy in the management of depressive disorders, speed of onset of action, side-effect profile, and toxicity in overdosage. In terms of effectiveness and speed of onset of action, available antidepressants do not differ significantly, but there is substantial evidence that they do have very different side-effect profiles, and that their toxicity in overdosage varies considerably.

Leonard (1986) has pointed to the considerable disparity in the lethality of overdosage of various antidepressants. Using Office of Population Censuses and

Surveys data, he tabulated the number of deaths, both intentional and accidental, reported in England and Wales for various antidepressants. When only one drug was taken, the numbers were: amitriptyline 750, dothiepin 376, imipramine 180, trimipramine 101, doxepin 59, maprotiline 58, clomipramine 30, and mianserin 23. These figures do not, however, take any account of the frequency of prescription of each. Assuming an average daily dose of 112 mg for 60 days for TCAs and 45 mg for 60 days for mianserin, and estimating the relative incidence from the amount of drug used, an estimated death rate was calculated per million patients treated for each antidepressant. The rates were: amitriptyline 166, dothiepin 147, maprotiline 115, imipramine 105, doxepin 99, trimipramine 93, clomipramine 34, and mianserin 15.

In the UK, the National Health Service system permits very accurate compilation of all prescriptions issued by GPs. Using such data, Cassidy & Henry (1987) calculated a Fatal Toxicity Index, on the basis of the number of deaths per million prescriptions issued for antidepressants during the years 1975–84 in England, Wales, and Scotland. They also calculated indices for a number of standard units and for gross quantities of drugs prescribed; all three methods in fact produced similar rankings for the drugs concerned.

Cassidy & Henry found that for all antidepressants combined, this Index was 34.9, but when the drugs introduced before 1970 (essentially TCAs) were compared with those in use since 1973, differences which were statistically highly significant were found (except in the case of maprotiline). The number of fatal poisonings observed and the numbers expected (in parentheses) for pre-1970 antidepressants were: dibenzepin 4 (0.9), desipramine 13 (5.7), dothiepin 533 (372), amitriptyline 1181 (886), nortriptyline 57 (51), doxepin 102 (114), imipramine 278 (342), trimipramine 155 (196), opipramol 2 (3.2), clomipramine 51 (160), protriptyline 6 (20), and iprindole 2 (8.9).

The Fatal Toxicity Indices (deaths per million prescriptions) were: dibenzepin 157.5, desipramine 80.2, dothiepin 50.0, amitryptyline 46.5, nortriptyline 39.2, doxepin 31.3, imipramine 28.4, trimipramine 27.6, opipramol 21.8, clomipramine 11.1, protriptyline 10.3, and iprindole 7.8. However, it should be noted that dibenzepin, desipramine, and opipramol are no longer extensively used in the UK by GPs. Similar calculations for deaths observed and expected from the MAOIs were: tranylcypromine 15 (9), phenelzine 24 (36.7), isocarboxazid 3 (8.2), and iproniazid 0 (0.97); this group of drugs is no longer widely used by GPs either, mainly because of tyramine incompatibility.

With the exception of maprotiline, the results for antidepressants introduced since 1973 were very different from those of the old TCAs. The deaths observed and expected were: maprotiline 83 (77), trazodone 6 (15), viloxazine 2 (7.4), butriptyline 1 (4.7), mianserin 30 (187), nomifensine 3 (42), and lofepramine 0 (3.7). The fatal toxicity indices were: maprotiline 37.6, trazodone 13.6, viloxazine 9.4, butriptyline 7.5, mianserin 5.6, nomifensine 2.5, and lofepramine 0.0.

Limiting the means of suicide

Though the factors which influence suicide rates are many, there is some evidence that changing prescribing habits or changing the availability of lethal substances has in the past influenced both patterns of suicide and the overall outcome of DSH. For instance, the reduction in the completed suicide rate in the 1960s may have been at least partly related to the replacement of barbiturates by benzodiazepines. Between 1964 and 1974, the numbers of suicides recorded as attributable to barbiturates used alone declined from nearly 1500 to less than 1000, while over the same period, prescriptions written for these drugs dropped by approximately 50%. Between 1968 and 1978, the number of prescriptions issued by GPs for barbiturates fell from 14.2 million to 5.1 million.

However, any consideration of the decline in UK suicide rates in the 1960s must also examine the question of changes in the nature of the domestic gas supply. The decline in the crude suicide rate began shortly after the beginning of the detoxification of domestic gas. Indeed, studies in some towns suggested that the sharp decline in the suicide rate between 1963 and 1970 was wholly due to a reduction in deaths due to gas (Kreitman, 1976). However, when the gas became 'safe', there was apparently no obvious switch from this to other methods. It has been suggested (Kreitman, 1976) that in some individuals, the scenario of suicide specifies the use of a particular method, and that if this becomes unavailable, actual suicide is less likely. In a review of explanations for the trends during the 1960s, Brown (1979) concluded that

> "the decline cannot at present be attributed with any confidence to attempts to alleviate the mental, emotional, social or spiritual state of potentially suicidal people. The most convincing evidence so far is in favour of fortuitous extraneous events ... (which) include the reduction in toxicity of domestic gas supplies, the reduced lethality of prescription sedatives, and improved treatment for self-poisoning".

Just as it was regarded as important to persuade GPs in the 1960s to limit their prescriptions of barbiturates, it may now be considered worthwhile to encourage them to prescribe new antidepressants which are safer than the old TCAs, given that the effectiveness of these drugs has been adequately demonstrated.

Conclusions

Depression is one of the commonest conditions seen and treated by GPs; antidepressants form the cornerstone of treatment, but the choice available is very extensive. Antidepressants do not vary in efficacy or speed of action, but do so appreciably in side-effect profile and in toxicity in overdosage. Since depression is frequently a cause of suicide and a factor in deliberate self-harm, and since poisoning, often with prescribed medication, is a common method of both suicide and DSH, GPs need to pay careful attention to the detection of suicidal risk. In particular, there should be concern about markedly depressed patients who remain in the community being issued with a prescription which provides the means of their self-destruction. Some antidepressants are clearly more toxic than others, and although it is recognised that factors implicated in suicide are complex, it would seem sensible if GPs preferentially used antidepressants with low toxicity. Such action might influence successful suicide rates, reduce the risk of DSH, and reduce the costs of the care of those who take overdoses.

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Tyramine and New Monoamine Oxidase Inhibitor Drugs

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The hypertensive crisis induced by the ingestion of cheese in subjects undergoing treatment with monoamine oxidase inhibitors (MAOIs) led to their virtual disappearance in many parts of the world. Three strategies to try and diminish the risk of this reaction have been developed: the combination of current (irreversible and non-selective) MAOIs with tricyclic antidepressants, the use of new selective MAOIs, and the use of new reversible MAOIs. The relative effectiveness of these different approaches can be assessed by the tyramine pressor test. The introduction of reversible and selective monoamine oxidase-A (MAO-A) inhibitors looks especially promising clinically.

Monoamine oxidase inhibitors (MAOIs) have had a chequered and controversial history. Iproniazid, the first to be recognised as an effective antidepressant, was widely heralded when it was introduced to psychiatry in the late 1950s, but dropped out of use after it was associated with liver damage. However, the major blow to MAOIs came when cerebrovascular accidents were linked to hypertensive crises – one of the most serious, even life-threatening complications of these drugs. Blackwell (1970), following the suggestion of the pharmacist-husband of a patient taking an MAOI, associated these crises with the ingestion of cheese – the 'cheese reaction'. In 1963, he reviewed 12 patients who had suffered a hypertensive crisis while taking MAOIs: one had also used amphetamines, while eight out of ten who were seen soon after the reaction recalled having eaten Cheddar cheese. He noted the similarities to hypertensive crises induced by phaeochromocytoma, and suggested a similar pharmacological reaction through the release of pressor amines. Blackwell further noted that amphetamines can provoke the release of noradrenaline, which could explain the hypertensive crisis of the patient who had taken that substance. Following Asatoor *et al* (1963), the cheese reaction was linked to its high tyramine content, and further animal research confirmed this theory (Blackwell, 1970).

Consequently, by the 1970s, as the list of prescribed interactions and dietary restrictions became more complex, MAOIs all but disappeared from the psychopharmacological armamentarium in many parts of the world. Nonetheless, some psychiatrists from the USA, but particularly in Great Britain, persisted in using them, and found that they benefited many patients who had responded poorly to other treatments. Over the ensuing decade, the efforts of a few clinical research groups helped to rescue these drugs from obsolescence, by finding them to be effective and drawing attention to some putative advantages over other agents (White & Simpson, 1985). However, two important matters remain unresolved: firstly, the indications for and effectiveness of MAOIs in depression, anxiety, and other disorders needed to be better delineated (Murphy *et al*, 1987); and secondly, strategies to avoid the hypertensive crisis had to be developed. Three approaches have been tried: the combination of current (non-reversible and non-selective) MAOIs with tricyclic antidepressants (TCAs), the use of selective MAOIs, and the use of short-acting, selective, reversible MAOIs. Tyramine pressor tests have been used to evaluate these approaches.

The tyramine pressor test

Tyramine exerts its pharmacological effects mainly independently by displacing noradrenaline from its intraneuronal stores (Burn & Rand, 1958). Modern pharmacological techniques have shown that tyramine binds at a site located on or within synaptic vesicles, but that it does not bind to post-synaptic receptors in the rat brain (Vaccari, 1986).

In animal pharmacological studies, tyramine has been used routinely for many years to assess the adrenergic interaction of drugs. In man, the tyramine test was reported in the early 1960s as a diagnostic tool in phaeochromocytoma, but its potential as a pharmacological method in clinical investigations was not fully appreciated until the 1970s (Ghose, 1984).

Tyramine produces several pharmacological effects, of which an increase in blood pressure after it is injected as an intravenous bolus provides the more reliable information. Tyramine sensitivity is usually defined as the amount of tyramine required to increase the systolic blood pressure by 30 mmHg, and this is determined from the dose response curve. Ghose (1984) standardised this test, and suggested an initial dose of 0.25 mg, followed by small increments of tyramine until the increase in blood pressure reaches this defined amount. Values in both normal controls and untreated depressives oscillate between 2 and 6 mg of tyramine (Mendis *et al*, 1981; Bieck & Antonin, 1982; Pare *et al*, 1982; Ghose, 1984; Pace *et al*, 1988). Pare *et al* suggested that 5–8 minutes was the normal delay that systolic blood pressure takes to return to baseline after an injection of tyramine. Bieck & Antonin (1982) gave tranylcypromine to six healthy volunteers, and showed that the increase in sensitivity to tyramine induced by this compound is more precisely measured when both the height and duration of the increase of systolic blood pressure are taken into account. When this was done, i.e. the area under the blood pressure curve was calculated, both height and duration were introduced into the calculation. In this way, the method was from four to ten times more sensitive than when only tyramine dosage was used. Thus, 40 mg of tranylcypromine increased tyramine sensitivity, measured by the dosage of tyramine, from 8–16 times (2–4 mg to 0.2–0.6 mg), while this sensitivity increased from 28 to 162 times when the height and duration of the increase in systolic blood pressure were measured.

Pickar *et al* (1981) used a continuous infusion pressor test; they added tyramine each 5–8 min until a rise of 30 mmHg in systolic blood pressure was reached and maintained for 5–8 min, the tyramine sensitivity being measured in mg of tyramine infused/min to produce this rise in blood pressure. They also took into account the time required for systolic blood pressure to return to half of baseline after cessation of tyramine: the normal value is 5 min. The advantages of bolus injection, as compared to continuous infusion, which were pointed out by Ghose (1984), have been confirmed by more recent work (Pace *et al*, 1988).

Tricyclic antidepressants produce a decrease in sensitivity to the tyramine pressor test. Clomipramine has been shown to have a markedly greater effect than maprotiline in diminishing the tyramine pressor response (Mulgirigama *et al*, 1977). However, there appear to be more risks associated with clomipramine (Beaumont, 1973) than with other TCAs, and this may well apply to all serotonin-affecting drugs (Graham & Ilett, 1988). Ghose (1984) suggested using not only this test, but also noradrenaline and phenylephrine pressor tests to evaluate whether the effect is due to blockade of uptake, or to post-synaptic α-receptor blockade, or both. Amitriptyline has both effects (Coppen & Ghose, 1978), but other TCAs have not been studied.

The augmentation in tyramine pressor effect induced by MAOIs may result from an increased release of pre-synaptic stores of noradrenaline, as a result of inhibition of degradation of MAOI action on intraneuronal MAO. Other mechanisms of potentiation may include impaired degradation of tyramine itself in the presence of MAOIs. Furthermore, certain irreversible MAOIs, such as tranylcypromine, may facilitate release of amines (Youdim & Finberg, 1985). There may also be some counterbalancing effects: some MAOIs, like TCAs, inhibit monoamine uptake. Prolonged treatment with MAOIs may result in down-regulation of post-synaptic adrenoceptors. There is also the question of 'false neurotransmitters', which are relatively ineffective post-synaptically, accumulating in the pre-synaptic stores and possibly accounting for the postural hypotension which has been common with MAOI treatment (Simpson & White, 1984).

In the clinical setting, the invariable route of tyramine administration is oral, and this raises the question of tyramine catabolism in the gut and liver. There have been estimates that less than 1% of tyramine passes unchanged into the systemic circulation (Faraj *et al*, 1981).

In fact, compared with the intravenous route, oral administration requires 100 times the dose of tyramine in unmedicated healthy subjects (Lader *et al*, 1970; Elsworth *et al*, 1978; Bieck *et al*, 1983). It is much easier and probably safer to study tyramine pressor effects in humans in the laboratory setting, using intravenous rather than oral administration of tyramine. Nevertheless, the distance of the intravenous test from the actual clinical situation casts substantial doubt on the clinical relevance of results obtained in such laboratory situations. Blackwell *et al* (1967) were pioneers in the use of oral tests when they gave 'Marmite' to two MAOI-treated patients, and measured their blood pressures. Lader *et al* (1970) claimed 400 mg of oral tyramine as the safe threshold in normal controls. Later, normal oral tyramine sensitivity was described as between 200–400 mg, whereas it is correctly defined as the quantity needed to induce an increase of 30 mmHg of systolic blood pressure (Bieck *et al*, 1983; Pare *et al*, 1985) or to induce either an increase of 20 mmHg of systolic blood pressure or a decrease of 10 beats/min of pulse frequency (Elsworth *et al*, 1978). The normal delay of systolic blood pressure to return to baseline is around 25 min (Pare *et al*, 1985).

Combination with tricyclics

The combination of classical MAOIs with TCAs has gained a reputation for both unusual efficacy and unusual toxicity, with possible effects including the induction of delirium, seizures, and hyperthermic crisis (White & Simpson, 1981). However, the two classes of drugs are claimed to be safe when started together – i.e. within the same 24-hour period – at low dosages, and then gradually increased together to a maximum of half that used with single-drug treatment. Adding small doses of an irreversible MAOI to an on-going course of TCA treatment may also prove reasonably safe. Substantial evidence exists, though, from case reports of hazards when a TCA is added to an established course of treatment with an MAOI (Razani *et al*, 1983). Though no studies provide firm support for a substantial advantage of combined treatment over other therapies

(White & Simpson, 1984), there is evidence that patients on the combined treatment may be less liable to hypertensive crisis than patients on irreversible MAOIs alone (see Cooper, this supplement).

Selective MAOIs

In human subjects, serotonin, adrenaline, and noradrenaline are predominantly deaminated by monoamine oxidase-A (MAO-A), while monoamine oxidase-B (MAO-B) deaminates phenylethylamine. This is a relative selectivity, since both noradrenaline and serotonin can be deaminated by MAO-B when MAO-A is specifically inhibited; many other monoamines are deaminated by both subtypes (Youdim & Finberg, 1985; Da Prada *et al*, 1988). Tyramine and dopamine are equally good substrates for both enzyme forms (Murphy *et al*, 1984; Da Prada *et al*, 1988). A promising new technique is the *in vivo* measurement of MAO brain activity of both enzymes by means of positron emission tomography (Fowler *et al*, 1987). Pharmacological studies in the human brain have shown that MAO-A is localised in the microvessels and neurons of the locus coeruleus, while MAO-B is present predominantly in neuronal cells of the dorsal raphe nucleus; astrocytes contain both subtypes throughout the cortex and brain stem (Konradi *et al*, 1987). Outside the brain, human placenta contains predominantly MAO-A, and platelets only the B subtype (Murphy *et al*, 1984); in the small intestine, subtype A outnumbers the MAO-B by 80/20 (Youdim & Finberg, 1985), but in liver, MAO-B predominates by 70/30 (Da Prada *et al*, 1988).

Clorgyline, an irreversible selective MAO-A inhibitor, has shown significant antidepressant activity (Wheatley, 1970), but the oral (Lader *et al*, 1970) and intravenous (Pickar *et al*, 1981) tyramine pressor tests showed that it has no safety advantage over the non-selective drugs, and it is no longer manufactured (Mann *et al*, 1984).

Deprenyl (or selegiline) is an irreversible MAO-B inhibitor; its levorotary isomer is more widely used because it is thought to have a more selective action. In addition to MAO inhibition, it also shows some blockade of noradrenaline and dopamine reuptake, inhibition of noradrenaline release and increase of dopamine release possibly related to its metabolism to amphetamine (Lam, 1987). It is believed that at a dose of less than 15 mg/day, L-deprenyl is a selective inhibitor, but at between 20 and 40 mg/day, it begins to have its other effects, especially inhibition of dopamine uptake and MAO-A inhibition (Mann *et al*, 1989).

Mendis *et al* (1981) carried out a bolus injection tyramine pressor test in seven depressive patients: the baseline tyramine sensitivity of 3.5 mg (range 2.5–6.5) decreased to 2 mg (1.5–5) after 15 mg/day of L-deprenyl for 2 weeks and to 2 mg (1–4) after 30 mg/day for a further 2 weeks. Pickar *et al* (1981), using a continuous infusion tyramine test, showed that two patients treated with 10 mg/day of deprenyl had a 1.7-fold increase of sensitivity to tyramine, whereas in seven patients, 30 mg of clorgyline induced an increase of 29 times. They repeated (Sunderland *et al*, 1985) the test in 11 depressed patients, finding that 10 mg induced a 3.7-fold increase, 30 mg a 6.5-fold increase and 60 mg a 22-fold increase.

Elsworth *et al* (1978) found that an oral tyramine test of 150 mg does not lead to hypertensive reactions in subjects receiving 10 mg/day of L-deprenyl. Indeed, in four normal controls, tyramine sensitivity showed little change from a baseline of 400 mg to 300 mg (range 200–400). However, a hypertensive response has been seen at the relatively low tyramine dose of 80 mg in a patient receiving 20 mg/day of L-deprenyl, after he had shown no such reaction to 320 mg of tyramine while unmedicated (Simpson *et al*, 1983). Thus, dosages even lower than 30 mg/day can induce enough inhibition of MAO-A to make ingestion of a meal rich in tyramine dangerous.

L-Deprenyl has been used to treat Parkinsonian patients (Birkmayer & Riederer, 1983), and preliminary data suggest some beneficial effect on Alzheimer's disease (Tariot *et al*, 1987). It has shown significant antidepressant activity (Mendlewicz & Youdim, 1983), especially in atypical depression (Mann *et al*, 1982; Quitkin *et al*, 1984; Mann *et al*, 1989), although Mendis *et al* (1981) found no difference from placebo in one double-blind trial, using 10 mg/day of L-deprenyl. To explain this lack of effect, they quoted Lipper *et al*'s hypothesis (1979) that MAO-A inhibition is more closely related to the antidepressant effects of MAOIs, and suggested that MAO-B inhibitors only possess antidepressant action at a dosage sufficiently large to cause some degree of MAO-A inhibition. Mann *et al* (1989) have recently completed a double-blind study showing that L-deprenyl does not have a statistically significant antidepressant effect after 3 weeks of treatment at doses of 10 mg/day, though at higher doses (averaging 30 mg/day) for 6 weeks, it is superior to placebo.

Thus, it seems that at low dosages (10 mg/day), L-deprenyl does not carry the risk of tyramine-induced hypertensive crisis, but that it lacks antidepressant activity. At higher dosages, it has both antidepressant activity and the risk of cheese reactions. The antidepressant activity of this compound may be due to its MAO-A inhibition, although other possibilities, such as the inhibition of dopamine re-uptake or its metabolism to amphetamine, cannot be ruled out (Mann *et al*, 1989). The possibility that it could have both an antidepressant effect and a lesser potential for the cheese reaction exists, but is unproven.

Reversible MAOIs

Several reversible MAO-A inhibitors have been used as antidepressants: moclobemide, cimoxatone, and brofaromine; the latter appears to possess antidepressant activity and to offer some protection against tyramine (Bieck *et al*, 1983). Moclobemide has perhaps been best studied up to now; it is a short-acting compound, and the recovery time ($t½$) of enzyme activity is about 16–20 h (Amrein *et al*, 1988). In experimental conditions, tyramine is able to displace moclobemide and/or its metabolites from the active site of the enzyme (Keller *et al*, 1987).

Moclobemide has shown antidepressant activity in open (Larsen *et al*, 1984; Kapfhammer *et al*, 1986) and in double-blind studies (Casacchia *et al*, 1984; Norman *et al*, 1985). Its therapeutic dosages ranged from 300 to 600 mg/day, with 450 mg as the upper dosage for out-patients and the average dosage for in-patients (Gieschke *et al*, 1988).

In the intravenous tyramine pressor test, therapeutic dosages of moclobemide have shown only a limited increase of sensitivity of 2- to 4-fold compared with baseline (see Table I) (Tiller *et al*, 1987; Korn *et al*, 1988*a*). When the test took place after only one dose of moclobemide (100–300 mg), the increase of tyramine sensitivity was maximum at 3 h and had virtually disappeared at 24 h (Korn *et al*, 1988a).

The results of the oral tyramine test were more interesting. Korn *et al* (1988*a*) found that the tyramine sensitivity was >200 mg in seven volunteers, and decreased to 100–200 mg after 2 weeks of 300 mg/day of moclobemide. The dose-pressor-response curve was shifted to the left by a factor of 4.1; this was greater than the intravenous curve, which only shifted by a factor of 2.4. Thus, the potentiation of the pressor effect of oral tyramine by moclobemide appears to be due to inhibition of the removal of tyramine by first-pass metabolism, as well as inhibition of tyramine metabolism by MAOI within adrenergic nerve terminals (Korn *et al*, 1988*b*).

TABLE I

Pressor effects of intravenously administered tyramine in normal patients and in depressed patients treated with moclobemide

Subjects	Dosage (mg/day)	Baseline	Treatment	Ratio
		(means ± s.d.[1] or s.e.m.[2])		
8 depressed[1]	280[3]	5.6±2.5	2.5±1.6	2.9±1.8
5 depressed[1]	390[4]	5.6±2.5	2.4±1.7	3.6±2.6
7 normals[2]	300	4.1±0.4	1.8±0.1	2.4±0.4
6 normals[2]	600	3.6±0.5	1.1±0.1	3.3±0.6

Ratio: tyramine dose drug free/tyramine dose on moclobemide

1. Tiller *et al* (1987).
2. Korn *et al* (1988*a*).
3. 280±90 mg/day.
4. 390±80 mg/day.

The same investigators (Korn *et al*, 1988*a*) also found that peak tyramine plasma concentrations and concomitant increase in systolic blood pressure were considerably smaller when oral tyramine was given together with a meal than when it was administered as a bolus with tap water. Six volunteers who received 300 mg/day of moclobemide for 2 weeks ingested tyramine (100–200 mg) with tap water, which produced a rise in systolic blood pressure of 65 ± 11 mmHg; when the same quantity of tyramine was ingested in a full meal, the systolic blood pressure increased 26 ± 10 mmHg. Results were similar when a double dose of moclobemide was used. Gieschke *et al* (1988) also found that when an artificially enriched meal of 50 or 100 mg of tyramine was administered to eight volunteers who received 450 mg/day of moclobemide, it did not lead to a clinically relevant change in blood pressure.

It is therefore recommended that moclobemide be administered at the end of a meal, in order to avoid tyramine absorption at a time when the drug reaches its peak concentration in the intestine (Korn *et al*, 1988*a*; Muller *et al*, 1988). In six volunteers, the amount of oral tyramine which produced an increase of 30–50 mmHg in systolic blood pressure was roughly doubled when moclobemide and tyramine were given together, instead of administering moclobemide 1 h before tyramine intake (Muller *et al*, 1988). These studies demonstrate that tyramine in quantities of up to 100 mg does not lead to clinically relevant blood pressure changes in moclobemide-treated patients, if the drug is taken at the end of the meal (Korn *et al*, 1988*a*).

Da Prada *et al* (1988) examined the content of tyramine in six copious, five-course meals in six European restaurants, and found that this ranged from 10 to 36 mg, which is well below the upper safe threshold for the use of moclobemide. It was concluded that normal quantities of wine and beer can be regarded as free of risk to patients taking moclobemide, and that they only have to avoid aged cheese or exclusive cheese meals.

Discussion

The complications of the cheese reaction led MAOIs almost to disappear from the psychopharmacological armamentarium in many parts of the world, but there is now a revival of this class of drugs, based on new scientific knowledge and on a new generation of compounds (Rafaelsen, 1988; Nutt & Glue, 1989).

Three strategies have been developed to avoid the hypertensive crisis produced by tyramine: the combination of current (non-reversible and non-selective) MAOIs with TCAs, the use of new selective MAOIs, and the use of new, reversible MAOIs.

Tyramine pressor tests are a useful clinical tool to assess the efficacy of these approaches. Intravenous and oral tests have been used: the latter approximates more closely to clinical reality, and this can become even closer when tyramine is administered with a full meal. These tests are more sensitive when both tyramine sensitivity (dosage of tyramine needed to increase the systolic blood pressure by 30 mmHg) and delay of systolic blood pressure to return to normal are measured.

The combination of TCAs with classical MAOIs decreases the possibility of a hypertensive crisis, but it is not completely safe. As expected, the combination of TCAs and a reversible MAO-A inhibitor also reduced the low increase of tyramine sensitivity produced by the former drug (Korn *et al*, 1986).

However, L-deprenyl, an irreversible predominantly MAO-B inhibitor, can still produce the cheese reaction at antidepressant dosages, because it also inhibits the A enzyme. On the other hand, moclobemide, a reversible MAO-A inhibitor, has been found to have only a slight effect on tyramine sensitivity. It can be safely used if administered at the end of a meal containing less than 100 mg of tyramine, and most meals in fact contain less than this quantity. Other reversible inhibitors appear to have similar properties, though perhaps to a lesser extent. Therefore, patients should still be advised not to eat *excessive* amounts of food high in tyramine, if they are taking one of the new generation of MAOIs.

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Tyramine and Irreversible Monoamine Oxidase Inhibitors in Clinical Practice

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The cheese reaction following use of the irreversible monoamine oxidase inhibitors (MAOIs) began to be reported in the UK with increasing frequency from about 1961. By 1965, the underlying mechanism (tyramine-provoked hypertension) had been essentially elucidated. Thereafter, this potentially severe side-effect could have been largely avoided by the use of fairly simple dietary precautions. Unfortunately, suspicion and fear burgeoned, and both the seriousness and the frequency of risk were dramatically inflated. This was a major factor in the subsequent general disuse of the irreversible MAOIs. Second-generation MAOIs which are selective for monoamine oxidase-A and B are now being synthesised and may eliminate the eventuality of hypertension without special dietary precautions.

The monoamine oxidase inhibitors (MAOIs) were introduced into psychiatry as a treatment for depression in 1957. In the UK they probably attained peak usage by 1965–1967, when seven of these drugs were available for prescription — iproniazid, nialamid, phenelzine, pheniprazine, isocarboxazid, mebanazine, and tranylcypromine. All were irreversible and non-selective inhibitors of monoamine oxidase-A and B (MAO-A, MAO-B) — though this was not known at the time — with cumulative and pervasive pharmacological effects lasting for up to 3 weeks beyond their elimination from the tissues.

Acute hypertension (mainly systolic) — the most alarming and potentially dangerous of several consequences of MAOI use — began to be reported with increasing frequency from 1961. Lurie & Salzer (1961) reported that two of 84 patients being treated with tranylcypromine experienced 'a devastating headache accompanied by a transient rise in blood pressure', and Clark (1961) discontinued an early trial with the same drug after encountering the condition in three of 30 patients. Brown & Waldron (1962) reported six similar cases amongst 150 patients in a general practice evaluation, while Lees & Burke (1963) noted this side-effect in 11 of 60 patients.

Hypertensive episodes following the use of phenelzine were reported by Dally (1962) and by Taylor (1962), but the drug was believed to be relatively safer in this respect than tranylcypromine. The sometimes paradoxical side-effects of MAOIs (e.g. profound hypotension and hypertension), occurring in the same individual at different times, suggested to some clinicians that exogenous elements, including certain foods and/or prescription drugs, might be implicated, but the precise relationship remained enigmatic.

Blackwell (1963) was the first to investigate in detail hypertensive crises following MAOI use. He reported 11 patients taking tranylcypromine (singly or in combination with trifluoperazine-parstelin) and one taking phenelzine, who developed severe throbbing headaches: typically, these commenced in the occipital region and later became generalised. Tachycardia and palpitations were common, and some patients experienced nausea and vomiting. Blood pressure was recorded in seven patients, and both systolic and diastolic values were greatly elevated. One patient suffered a subarachnoid haemorrhage, one a hemiplegia for 6 weeks, and one died following intracranial haemorrhage. Seven patients had ingested cheese between 40 minutes and 2½ hours before the attack.

Six months later, Cooper *et al* (1964) published data on 36 of 146 patients (25%) who had been treated for depression with tranylcypromine (singly or in combination with trifluoperazine) and who had been similarly afflicted. Fifteen were monitored during an attack, the blood pressure being recorded until it had returned to normal: this elevation was from a mean of 123/79 to 183/116 mmHg (corresponding to a systolic increase of 49% and a diastolic of 32%). Three subjects suffered proven cerebral haemorrhage. Ten patients had ingested cheese 1–3 h prior to the episode, and one had undergone a methylamphetamine abreaction (20 mg) immediately before.

The role of cheese

Careful, if limited, clinical observations, including those referred to above, pointed towards cheese as a possible cause or co-factor for these reactions. However, not all individuals who had eaten cheese developed high blood pressure, and some had become hypertensive after ingesting other nutriments (e.g. 'Marmite', a yeast extract) or certain beverages (e.g. beer and red wines), suggesting that the provoking agent(s) might be more widely distributed. However, for a number of theoretical reasons, it was conjectured that tyramine was the most likely culprit.

Tyramine

Tyramine was the first known substrate of monoamine oxidase (Hare, 1928). The high concentration of this enzyme in the intestinal mucosa (Levine & Sjoerdsma, 1962), and the presence of pressor amines in the gut as a result of bacterial decarboxylation of amino acids (Melnykowycz & Johansson, 1955), suggested that one biological function of MAO might be detoxification (Blashchko, 1952). Because of the low pH and restricted time for bacterial action, the amounts of amine produced in the gut are probably small, but adverse effects resulting from amine absorption were a theoretical possibility.

Many of the pressor amines were originally isolated from products of putrefaction, and cheeses which are ripened over long periods of time fall into this category. During maturation, casein in cheese is broken down under the influence of rennet and bacterial action into peptides and free amino acids, while tyramine may be formed from tyrosine. The latter was itself isolated from cheese, and subsequently named after the Greek (Tyros) for cheese.

Blackwell & Mabbitt (1965) and Horowitz *et al* (1964) were among several investigators who conducted chemical analyses on cheeses and other foods to determine their tyramine content. Both groups noted that the tyramine content of different cheeses and even generically similar cheeses (e.g. English cheddars) varied enormously, depending on a number of factors. These included:

(a) The concentrations of tyrosine and tyrosine decarboxylase in the maturing cheese.

(b) The presence of bacteria with tyrosine decarboxylase activity (e.g. coliforms and streptococci group D).

(c) The manufacturing process (especially heat treatment), which may reduce the number of organisms and enzymes available during maturation, though this may be offset by contamination with both types of organism, due to faulty hygiene.

(d) The addition to the cheese milk of starter micro-organisms (e.g. streptococci group N), which compete with the tyrosine decarboxylase organisms.

(e) Time of ripening — long matured cheeses (more than 3 months) such as cheddar, tending to have higher concentrations of tyramine.

Thus, in an individual cheese, the final tyramine content on maturation will be determined by the algebraic sum of the several facilitatory and inhibitory influences enumerated above; and these may themselves vary greatly, depending on pervasive circumstances. To further complicate matters, it is not completely certain which group of bacteria is the most important in promoting tyramine formation.

Table I, synthesised from Blackwell & Mabbitt (1965) and Horowitz *et al* (1964), shows the tyramine content of several typical English, American, and European cheeses. Data on flavour are also displayed; these indicate that olfactory and gustatory evidence of putrefaction do not necessarily equate with a high tyramine content, which can only be gauged accurately by chemical analysis. However, different (older) methods sometimes yielded discrepant results for the same cheese.

Newer techniques, which are more accurate and reproducible, have generally assayed lower concentrations. Indeed, Da Prada *et al* (1988), using refined modern procedures, have reliably measured the tyramine content of many different foods. They found that no item contained more than 1 g tyramine/kg and only a few contained more than 500 mg/kg (some cheeses, one kind of salami, and one sample of dried meat). In part, these lower values probably reflect more recent and hygienic food processing methods. Nearly all of the earlier hypertensive crises were reported in the UK, though MAOIs were then in widespread use in both Britain and the USA. At that time, the annual cheese consumption per head in the two countries was approximately the same — about 3.85 kg (8½ lb) and 4.5 kg (10 lb) respectively — but the greater popularity of cottage and cream-type cheeses in the USA may have partly accounted for the differences between the two countries in numbers of reactions (Blackwell & Mabbitt, 1965). Tyramine-rich cheeses were thus identified as being capable of provoking acute hypertension in MAOI-treated patients. However, subsequent studies confirmed high concentrations of tyramine in several foods, including marmite, yeast and meat extracts, certain wines (e.g. red chianti), and pickled fish; all of these had apparently elevated the blood pressure in subjects receiving MAOIs. Moreover, other naturally occurring amino acids and amines (e.g. dopamine in broad bean pods, tryptophan, and tryptomine), present in variable amounts in a number of foods, were found to be culpable occasionally, while histamine, which is present in high concentrations in marmite, was observed to cause headache in MAOI-treated patients without increasing the blood pressure (Cooper, 1967).

Mechanisms of the interaction of tyramine with MAOIs

The clinical significance of the interaction of irreversible MAOIs with tyramine is an enhanced ability of the amine to increase systolic blood pressure. This is largely due to the inhibition of intraneuronal MAO-A activity

TABLE I

Tyramine content of cheeses purchased in the UK and USA

			Tyramine hydrochloride (µg per g)	
No. of cheese[1]	*Variety of cheese*	*Flavour*	*By chromatography*	*Method of Kosikowsky & Dahlberg (1950) Colorimetric*
1	English Cheddar	Mild, buttery	182	
2	English Cheddar	Acid, buttery	72	
3	English Cheddar	Very mild	332	
4	Westcountry (farmhouse)	Very acid, slightly fruity, coliform flavour	284	
5	English Cheddar	Mild	281	
6	English Cheddar	Acid, bitter	480	
7	English Cheddar	Acid, mature	0	
8	English Cheddar	Goaty, mature	953	1620
9	Canadian Cheddar	Acid, cowy, off flavour	231	
10	Canadian Cheddar	Clean, mature	535	
11	New Zealand Cheddar	Very bitter, unpleasant	580	
12	New Zealand Cheddar	Rancid	417	
13	Australian Cheddar	Mild, slightly bitter	226	
14	Kraft (cracker barrel)	Mild, slightly bitter	214	
15	Wensleydale	Mild, slightly bitter	ND	0
16	Wensleydale	Mild, slightly bitter	ND	132
17	Cheshire	Mild, slightly bitter	ND	90
18	Cheshire	Mild, slightly bitter	ND	216
19	Cheshire	Mild, slightly bitter	ND	84
20	Caerphilly	Mild, slightly bitter	ND	138
21	Caerphilly	Mild, slightly bitter	ND	0
22	Caerphilly	Mild, slightly bitter	ND	0
23	Camembert		86	
24	Stilton		466	
25	Brie		180	
26	Emmentaler		225	
27	NY State Cheddar		1416	
28	Gruyere		516	
29	Processed American		50	
30	Cream		ND	
31	Cottage		ND	

1. 1–22: Cheeses purchased in the UK; 23–31: Cheeses purchased in the USA.
ND = not detected.

in noradrenergic sympathetic nerve endings, which has complex effects on the tyramine–noradrenaline interaction. However, the net result is higher intraneuronal concentrations of tyramine and greater quantities of 'protected' noradrenaline being made available for release by the nerve terminal. In addition, MAOIs increase the steady-state concentration of cytoplasmic noradrenaline, which is normally very low and is available for efflux from the neuron, as soon as tyramine increases the availability of the amine transporter on the cytoplasmic side of the cell membrane.

During MAO inhibition, there is a greater increase in the potentiation of the pressor effect of oral tyramine, compared to intravenous tyramine. This is due to an additional reduced presystemic deamination of tyramine in the gastrointestinal tract by MAO-A.

In a previously MAOI-treated individual, 10–20 mg of tyramine from cheese or some other foodstuff that has been ingested, is capable of provoking severe hypertension. For a non-treated person under experimental conditions, more than 500 mg is necessary to elevate systolic pressure by 30 mmHg (TYR 30, i.e. the amount of tyramine necessary to elevate systolic blood pressure by 30 mmHg) and in a real-life situation, more than 1000 mg. A generous five-course meal, without restriction, is likely to contain approximately 50 mg of tyramine.

The irreversible MAOI drugs

Initial clinical observations suggested that tranylcypromine was more likely to be associated with a hypertensive episode than the other MAOIs. However, it was not clear whether this impression was spurious, simply reflecting greater usage, or whether the drug was intrinsically a more potent enhancer of the pressor action of tyramine. In fact, recent studies on healthy subjects, during which the tyramine sensitivity factor (TSF = TYR 30 placebo/TYR 30 drug) of a number of MAOIs was determined, showed tranylcypromine to have a TSF at least twice that of phenelzine at an equivalent antidepressive dose (Table II).

These data thus provide experimental verification of tranylcypromine's extremely high potency to provoke a cheese reaction. TSF data, which have been found to be independent of age and the presence of a depressive illness, are not available for all MAOIs, but it is most unlikely that any compound, current or to be developed in the future, would have a greater TSF than tranylcypromine.

MAOIs and tricyclics combined

To effect its action, tyramine must be taken into the noradrenergic varicosity by the neuronal re-uptake mechanism. If this mechanism is inhibited, then theoretically, the tyramine could not cause noradrenaline release and, therefore, blood pressure would remain stable. In support of this, Kline *et al* (1981) showed that desmethylimipramine protected both acutely and chronically MAOI-treated rats against the increase of blood pressure induced in a tyramine test. Based on this finding, a clinical trial by Pare *et al* (1982) compared results from tyramine tests on normals, untreated depressed patients taking classical MAOIs, and patients taking MAOIs plus amitriptyline, trimipramine, or dothiepin (Table III). As predicted, five patients receiving an MAOI alone had a ten-fold enhanced sensitivity to tyramine. The six patients who also received amitriptyline had a sensitivity similar to the normals and untreated patients, but they did have a delay in the return of the systolic blood pressure to baseline. The six patients treated with MAOIs and dothiepin or trimipramine had a sensitivity and delay of return to baseline which was similar to the MAOI patients. The lack of action of the latter compounds was explained as being due to lower plasma levels, compared to amitriptyline, as shown by the correlation of tricyclic antidepressant (TCA) plasma levels with tyramine pressor sensitivity (Ghose *et al*, 1976), and more potent inhibition of noradrenaline uptake by amitriptyline. These authors pointed out that the intravenous tyramine test involved only 3 mg of tyramine, and that amitriptyline might not protect patients on MAOIs who ingested a meal of cheese, which could contain 50 mg of tyramine.

Pare *et al* (1985) then carried out an oral tyramine challenge test in ten depressed patients treated with combined MAOIs and TCAs; they found four patients who gained significant protection from oral tyramine (100 mg), and six who remained susceptible to

TABLE II

TSFs obtained with oral tyramine tests with different MAOIs

Drug	*Dose/day*	*TYR 30 Dose (mg)*	*TSF*[1]	*Range*
Tranylcypromine	20 mg	16	34 (±7)	
Phenelzine	45 mg	28	14.5	3.3–44
Deprenyl[2]	5 mg	141	5.4	1–17.5
Moclobemide[3]	3×200 mg	80	5.6	3.5–9.4
Moclobemide	3×100 mg	72.5	4.4	2.9–5.6
Moclobemide	3×100 mg	133	3.5	2.8–10

1. $\text{TSF} = \frac{\text{TYR 30 Placebo}}{\text{TYR 30 Drug}}$

2. At this dose, selective MAO-B. At effective antidepressant dosage (30 mg/day) deprenyl is non-selective.

3. Partial and selective MAO-A currently under development.

TABLE III

Pressor effects of intravenously administered tyramine in normal patients and in depressed patients, untreated and treated with MAOIs alone and in combination with TCAs

	Tyramine[1] (mg) mean and range	*Delay[2] (min) mean and range*
20 normals	3.6 (2.5–6.0)	
20 untreated depressed	3.4 (1.2–6.5)	
6 untreated depressed		5.8
5 patients on MAOI	0.3 (0.1–0.7)	20 (13–>20)
6 patients on MAOI+Dot/Tri[3]	0.8 (0.5–1.5)	20 (12–>20)
5 patients on MAOI+Ami[4]	3.0 (2.0–5.0)	20 (17–>20)

1. Dose required to increase systolic blood pressure by 30 mmHg.
2. Time needed for systolic blood pressure to return to baseline.
3. Dot/Tri: dothiepin or trimipramine.
4. Ami: amitriptyline.

From Pare *et al*, 1982.

15–50 mg. It was concluded that despite the earlier claims of safety, no combined regimen can, at present, be relied on to be totally free from the cheese effect, and that no relaxation of diet in patients taking both MAOIs and TCAs should be recommended.

Simpson *et al* (1983) found that the protective effect of amitriptyline against oral tyramine may be dosage-related. One of these patients showed no increase of reactivity to tyramine when he received 150 mg of amitriptyline together with tranylcypromine, but did when taking only the latter drug. However, another patient taking tranylcypromine was not protected from a hypertensive crisis by 100 mg of amitriptyline. In general, there is evidence that this combined strategy can be successful and, used as recommended, could be safer than conventional MAOIs used alone. However, it is insufficiently reliable to be generally advocated as a safeguard against the cheese reaction.

Other factors

Though tyramine was clearly established as being of overwhelming importance in the pathogenesis of the cheese reaction in MAOI-treated patients, it was suggested that a number of subordinate, more variable and subtle elements might also be involved. Thus, Davidson *et al* (1984) believed that habitus was significant, with mesomorphs being at lower risk than ectomorphs, while Dally (1967) reported a greater risk in non-endogenous depression and in patients who displayed a propensity to develop marked side-effects to other psychotropic drugs.

The impact of the cheese reaction on diets and MAOI usage

By 1965, for practical purposes, the cheese reaction had been largely elucidated, and had the resultant knowledge been disseminated widely, the incidence of hypertensive episodes could have been lowered to perhaps 1%, without limiting the use of the drugs and with little dietary inconvenience. However, both the extent and the size of the hypertensive risk were dramatically inflated by regulatory bodies, and tyramine-restricted diets proliferated. With little or no supporting evidence, some 70 food items were prohibited from patients being treated with irreversible MAOIs. Table IV, derived from Sullivan & Shulman (1984), summarises the findings from a survey on MAOI diets conducted in 22 psychiatric hospitals in Canada, the USA, Europe, and Australia. Foods were categorised into five groups, according to frequency of restriction: a total of 70 items was prohibited. Over 75% of the diets banned seven nutriments — wine, cheese, non-fresh fish, liver, yeast extracts, broad beans and beer, while all 20 diets restricted the first three foods.

Table V indicates the tyramine content of 18 restricted foods, with the source references on which the diets were based. It is clear that many diets were formulated on extremely dubious grounds, presumably because of an exaggerated fear of a cheese reaction. The source references actually suggest that only aged cheese, pickled herrings, concentrated yeast extract (e.g. marmite), and broad bean pods, need to be totally avoided.

The extreme tediousness of adhering to such

TABLE IV
Frequency of foods restricted on MAOI survey diets

Type of food	*100%*	*75–99%*	*50–74%*	*25–49%*	*0–24%*
Alcohol	Wine	Beer	Other alcoholic beverages		
Cheese and milk products	Aged cheese		Sour cream Yogurt	All cheese including cottage and cream cheese	Chocolate milk Tinned milk Buttermilk Ice cream
Meat, fish and poultry	Non-fresh fish	Liver	Fermented sausage Processed canned, pickled or aged meats		Caviar Snails Anchovies Game Pheasant Aged game
Fruits and vegetables		Broad bean pods	Bananas, avocados, figs & raisins	Banana peels Broad beans	Prunes Pineapple Plums Raspberries Oranges Other beans lima kidney soy Ripe tomatoes Egg plant Corn Pickles Sauerkraut Snow peas
Miscellaneous		Yeast extracts	Meat extracts Dried soups Bases & cubes Soy sauce Chocolate Improperly stored foods	Coffee Tea Cola drinks	Meat tenderisers Vinegar Marinade Salad dressing Vanilla baked goods Liquorice Cyclamates (excess) Nuts Carbonated beverages

From Sullivan & Shulman, 1984. Published by permission of *Canadian Journal of Psychiatry*.

impossible diets, coupled with the ubiquitous fear of a hypertensive episode, were two reasons contributing to the steady decline in use of the MAOIs in the later 1960s. However, this was compounded and accelerated by the results of major clinical trials from the USA (e.g. Greenblatt *et al*, 1964) and the UK (Medical Research Council, 1965). These were published shortly after the cheese reaction had reached maximum notoriety; they pronounced these drugs as inferior to both ECT and the TCAs (imipramine and amitriptyline), and no better than placebo.

The twin indictments of being 'dangerous and ineffective' (which was premature and mainly erroneous) almost ended the general use of the MAOIs, and also dramatically curtailed pharmaceutical research, though some psychiatrists, particularly in the UK, continued to prescribe these agents with good effects and without serious hazards.

TABLE V

Tyramine content of foods restricted on diets

Food	*Surveyed rate of restriction (%)*	*Tyramine content*[1] *µg/g or µg/ml*	*Tyramine content*[1] *mg per serving*
Cheese	100	Nil–2170	Nil–130.2 (60 g)
Fish (non-fresh)	100	Nil–3303	Nil–198.2 (60 g)
Wine	100	Nil–24.25	Nil–3.0 (120 ml)
Yeast extracts	95	66–2256	1.9–67.8 (30 g)
	90	1.8–11.22	0.6–4.0 (360 ml)
Broad beans	85	Active substance dopamine in pods[2]	—
Liver (fresh)	80	0.9–5	0–0.9 (90 g)
Other alcohol	70	—[2]	—
Sour cream	70	—[2]	—
Bananas (pulp)	65	7	1.0 (1 med. size)
Meat extracts	65	95–304	—
Aged meats	60	ND–1237	ND–73.8 (60 g)
Figs/raisins	60	—[2]	—
Soy sauce	60	1.76	Trace
Avocado	55	23	2.5 (½ med. size)
Chocolate	55	Active substance phenylethylamine[2]	—
Yogurt	55	—[2]	—
Dried soups, bases, or cubes	55	—[2]	—

1. Horowitz *et al* (1964), Blackwell & Marley (1969), Sen (1969), Boulton *et al* (1970), Rice *et al* (1975).
2. No documentation of tyramine content.

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Discussion

Currently, though, the MAOIs are being reassessed. Recent studies have suggested that the standard drugs (phenelzine, tranylcypromine, isocarboxazid) are more effective as treatments for depression than was believed hitherto (Quitkin *et al*, 1979; Ravaris *et al*, 1980), and that they are equivalent (or superior in certain subtypes — Ravaris *et al*, 1976; Liebowitz *et al*, 1984) to the TCAs, with fewer general side-effects. However, despite the new evidence, fear of the cheese reaction remains, and is a major deterrent to the widespread use of these compounds, especially in long-term therapy, when compliance is necessary for maximal benefit (Cooper, 1987).

The rise, fall, and rediscovery of the MAOIs is an object lesson to psychiatry. It teaches how potentially useful drugs can be prematurely condemned as ineffective and hazardous on limited and incomplete evidence. The cheese reaction (tyramine-provoked hypertension), which was essentially elucidated by 1965, could thereafter have been largely avoided by the use of a few dietary precautions, without restricting use of the drug. Instead, it was allowed to engender suspicion and fear, and was an important factor in the subsequent general disuse of the irreversible MAOIs. However, second-generation MAOIs, which are selective for MAO-A and B, are now being synthesised, and should eliminate the risk of hypertension, without any special dietary precautions. If these agents are shown to be therapeutically equivalent to the TCAs, their superior tolerance, and fewer side-effects, should give them distinct advantages in the drug treatment of depression.

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Antidepressants in Panic Disorders

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The efficacy of antidepressants for panic disorders has had major effects on our understanding of the classification, pathophysiology, and treatment of anxiety disorders. Psychiatric practice has also been significantly affected, but important issues remain unresolved, such as the mechanisms of therapeutic effect, optimal duration of therapy to minimise relapse, and the interaction and sequencing of medication with cognitive behavioural treatments.

Discovery of the efficacy of antidepressants for panic disorders has had a major impact on the classification, pathophysiological models, and treatment of anxiety. However, continued uncertainty remains about how antidepressants exert their therapeutic effect in panic disorders, the relative indications for one class of drugs or another, and the proper interdigitation of pharmacological and psychological approaches. These issues are examined in this paper in respect of three major classes of antidepressants – tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), and serotonin (5-HT) re-uptake blockers – all of which have been found to be effective for panic disorders, as well as several antidepressants that appear ineffective.

Definition of panic disorders

Panic disorders are considered here to encompass conditions characterised by the occurrence of spontaneous panic attacks, at least at the onset of the illness. These are limited to the DSM–III-R diagnoses of panic disorder and panic disorder with agoraphobia. Other anxiety and phobic states such as generalised anxiety disorder, and social and simple or specific phobias, will not be considered here, except as points of contrast.

Tricyclic antidepressants

Efficacy data

Imipramine

The TCA most investigated in the treatment of panic disorders is imipramine. As studies of imipramine in panic disorder have recently been reviewed elsewhere (Liebowitz, 1985; Fyer & Sandberg, 1988; Liebowitz *et al*, 1988*a*; Liebowitz, 1989), they will only be summarised briefly here.

The preponderance of available evidence suggests that imipramine is in fact effective in treating panic disorders; its efficacy for panic disorder with agoraphobia was first suggested by Klein's studies in the 1960s (Klein, 1964). Recent affirmative controlled studies include: two by Zitrin *et al* (1980, 1983) showing imipramine's superiority to placebo in panic patients who were also receiving behaviour therapy, findings of the superiority of both imipramine and phenelzine, as compared to placebo, in patients with 'endogenous anxiety' (panic disorders) by Sheehan *et al* (1980), and studies by Mavissakalian *et al* (Mavissakalian & Perel, 1985; Mavissakalian & Michelson, 1986) showing a high rate of response in patients with panic disorders receiving 150–200 mg/day of imipramine, but a poor response among those on smaller doses. Telch *et al* (1985) compared imipramine and placebo, and also examined the effect of instructions on anti-exposure in the imipramine patients. They found superiority of imipramine over placebo, but only in the presence of exposure instruction. Marks *et al* (1983) reported a 2 × 2 study comparing imipramine v. placebo and therapist-aided exposure v. relaxation, finding no efficacy for imipramine. However, this one negative finding may be due to low dosage of imipramine (158 mg/day on average at week 14, and 110 mg/day at week 26); the taking of patients unresponsive to imipramine into the study, and categorising rapid imipramine responders who terminate prematurely as 'early drop-outs'.

So far as open studies are concerned, Garakani & Klein (1984) found imipramine to be of benefit in patients with panic disorder who had no agoraphobic features. A naturalistic study (Aronson, 1987) of 60 patients found a good-to-excellent response in 29, which was 48% of the overall sample, but 88% of the 33 patients who tolerated imipramine. Thirteen of the 27 patients who terminated prematurely did so due to jitteriness in the first weeks of treatment, suggesting (see below) either too high an initial dosage or too rapid an elevation of dosage. A naturalistic study by Noyes *et al* (1989) found similar response rates and differences among panic patients who are compliant with an imipramine regimen, and in the sample as a whole.

Other tricyclics

Lydiard (1987) found in an open trial that desipramine was effective for panic patients, as did Gloger *et al* (1981) in 75% of 20 patients with panic disorder or panic disorder with agoraphobia who were given clomipramine. A recently reported placebo-controlled trial of clomipramine in agoraphobic patients also found a significant effect of the TCA on panic attacks and agoraphobic symptoms (Johnston *et al*, 1988). Interestingly, in both clomipramine studies, dosages of less than 100 mg/day were generally effective; desipramine above 200 mg/day (Lydiard, 1987) and imipramine above 150 mg (Mavassakalian & Michelson, 1986) are usually thought necessary to treat panic disorders. It is possible (see below) that clomipramine's greater serotonin re-uptake blocking effects may add to its potency.

Other TCAs, such as amitriptyline, nortriptyline, doxepin, and protriptyline, have so far received little or no study in panic disorders, though Tyrer *et al* (1988) recently studied dothiepin, with modestly positive results, as discussed below.

Heuristic issues

Klein's (1964) original observation that imipramine blocked panic attacks but not anticipatory anxiety, and that standard benzodiazepines did the reverse, contributed substantially to the DSM–III subdivision of anxiety neurosis into panic disorder and generalised anxiety disorder. Although widely hailed as useful for both clinical practice and research, the distinction between panic disorders and generalised anxiety disorder has been challenged by several recent findings. One is that imipramine was found to be as helpful as chlordiazepoxide in a sample of primarily anxious patients (possibly generalised anxiety disorder, though gathered prior to DSM–III), even after the panic subset (15%) was retrospectively removed (Kahn *et al*, 1986). More recently, Tyrer *et al* (1988) found the TCA dothiepin to be superior to diazepam in treating dysthymic, generalised anxiety, and panic disorders, with the effects of treatment independent of the original 'neurotic' diagnosis. Also, high-potency benzodiazepines, such as alprazolam (Ballenger *et al*, 1988), have been shown to block panic attacks. In a multicentre trial comparing alprazolam and placebo in patients with panic disorder or agoraphobia with panic attacks, after 4 weeks, 50% of the patients on alprazolam v. 28% of patients on placebo were free of panic attacks.

The study by Tyrer *et al* (1988) has been criticised (Klein, 1988) for using sub-optimal doses of TCA with regard to panic treatment, and for generalising from an atypical TCA to the whole class of drugs. However, what may distinguish the effects of imipramine and benzodiazepine respectively in the various anxiety disorders is the issue of relative potency. While imipramine and chlordiazepoxide appeared equipotent for generalised anxiety disorder-like patients, in the same protocol, imipramine was found to be superior for panic patients (Kahn *et al*, 1986). Similarly, standard benzodiazepines, such as diazepam and chlordiazepoxide, seem to be more potent for generalised anxiety than for panic attacks, although definitive proof of this must await the conclusion of further controlled trials.

The effects of imipramine in agoraphobic patients also suggested that panic attacks were the primary disturbance in most such patients, with anticipatory anxiety and agoraphobic avoidance following as reactions to having had the initially unexpected anxiety episode (Klein, 1964). As recently reviewed by Fava *et al* (1988), several subsequent investigations have generally affirmed this phenomenological sequence. Fava *et al* themselves, however, found that out of 20 patients suffering from panic disorder with agoraphobia, 18 reported experiencing agoraphobic avoidance, generalised anxiety and/or hypochondriacal fears and beliefs during the six months before the first panic attack. Normal controls reported significantly less of these phenomena in the 6-month period before an identical interview. It was concluded from these data that agoraphobic symptoms are more central to the disorder than are panic attacks, because they preceded them – in reverse of the causal sequence assumed in DSM–III-R.

Limiting the usefulness of these data, however, are two important methodological issues. Firstly, it is unclear whether both the patients and controls were asked about their prior symptoms with the interviewers blind to diagnosis. Secondly, the degree of agoraphobia, generalised anxiety, or hypochondria found in the patients prior to the onset of panic attacks is not specified. While it appears to have exceeded some particular threshold, and therefore differed from what was found in the controls, the investigators do not specify whether the patients suffered clinically severe agoraphobic features before their panics began, or whether these developed only after the onset of panics. Fava *et al* cite Weissman & Merikanga's (1986) finding that a sizeable percentage of agoraphobic patients in epidemiological samples did not have panic attacks, without specifying that many of them had limited symptom attacks, i.e. partial panic attacks. This does not appear to have been investigated in the sample of Fava *et al*.

Clinical issues

The efficacy of TCAs has revolutionised the treatment of panic disorders, contributing to the popularisation of medical models for treatment and of biological models for understanding these disorders. Aronson's (1987) study suggests that many panic patients are sensitive to TCAs initially, and require small initiating doses

(10–25 mg/day) to avoid feeling increased anxiety and jitteriness. Also, the relapse rate after discontinuation of the drug following 6–12 months of treatment is uncertain, with reports varying from 30–35% (Zitrin *et al*, 1983) to in excess of 75% (Sheehan *et al*, personal communication). Whether longer treatment would decrease the rate of relapse is unstudied, but it does appear that for at least some patients, imipramine treats rather than cures panic disorders.

How does imipramine compare with other treatments for panic disorders? Important data on this issue have recently been collected. Sheehan (unpublished data) completed a study comparing imipramine, alprazolam, phenelzine, and placebo in patients with panic disorders, finding high response rates for all three active drugs, with perhaps a slight advantage for phenelzine. The second phase of the cross-national study, comparing alprazolam, imipramine, and placebo (as yet unpublished), found both active drugs to be similarly effective after 8 weeks, although alprazolam showed efficacy more quickly. This was also noted by Charney *et al* (1986) in a comparison of the anti-panic effects of imipramine, alprazolam, and trazadone. Versiani *et al* (1989) have also found high rates of response for imipramine, alprazolam, clomipramine, and tranylcypromine in panic disorders. Mavissakalian & Michelson's (1986) study suggests that in sufficient dosages (150 mg/day or more), imipramine substantially adds to the efficacy of either flooding or programmed practice in agoraphobic patients. Still to be done are direct comparisons of imipramine with a cognitive-behavioural treatment that focuses both on panic attacks and on avoidance. Also of interest is whether combined drug-behavioural treatment would reduce relapse after discontinuation of the drug. In a departure from the past, studies to answer such questions are now being undertaken by combined teams of established psychopharmacological and cognitive behavioural investigators, which is providing greater expertise and credibility than if the studies were undertaken solely by one discipline or the other.

Therapeutic mechanisms

One still debated issue is whether concomitant exposure is necessary for the anti-panic effects of imipramine. Findings of efficacy in pure panic disorder without phobic avoidance (Garakani & Klein, 1984) suggest not, but Telch *et al*'s (1985) finding of no efficacy for imipramine in the presence of anti-exposure instructions reasserted the issue. This latter study has been criticised, however, for its small sample size and questionable panic ratings.

Marks *et al* (1983) hypothesised that TCAs help agoraphobics principally by alleviating depression. As evidence, they cite findings that panic studies in which the effect of imipramine exceeded that of placebo contained more depressed patients than their own negative study, and that antidepressant effects usually parallel anti-phobic effects. Arguing against Marks' position are: (a) Johnston *et al*'s (1988) positive clomipramine study in panic patients with low baseline depression; (b) a study where baseline depression was a negative predictor of the responsivity of agoraphobic patients to imipramine (Zitrin *et al*, 1980); (c) another where it did not correlate with outcome (Sheehan *et al*, 1980); (d) the benefit of imipramine in non-depressed panic patients (Garakani & Klein, 1984); (e) the low incidence of dexamethasone non-suppression in panic disorders (Curtis *et al*, 1982); (f) the seeming lack of efficacy of TCAs in simple phobics (Zitrin *et al*, 1983), and perhaps also in social phobics, who differ from agoraphobics more in not having spontaneous panic attacks than in their level of depression.

Tyrer (Tyrer & Shawcross, 1988; Tyrer *et al*, 1988) has argued that both TCAs and MAOIs have a general patholytic effect in anxiety, depression, and panic, and therefore that the anti-panic effects of these drugs do not support a distinction between panic disorders and generalised anxiety disorder. The limitations of these arguments for TCAs have already been discussed, but there may be more of a case for broad effects of MAOIs, as discussed below.

Another viewpoint focuses on cognitive factors in patients with panic disorders. 'Radical cognitivists', i.e. those who see the problem almost entirely in cognitive terms, argue that affected patients grossly over-react to normal physical sensations, giving catastrophic interpretations to everyday sensations of dizziness, skipped heart beats, etc. (Beck & Emery, 1985). To the degree that this school acknowledges the efficacy of TCAs in panic disorders, it would at least have to posit a drug effect on normalising cognitive style. More 'moderate' cognitive behaviourists, however, favour a mixed bio-psychological model for panic, in which quantitatively or qualitatively abnormal physical sensations (lightheadedness, spontaneous tachycardia, etc.) are then over-reacted to. In this model, cognitive treatments are aimed at reducing the tendencies to a catastrophic reaction, while drug effects could be seen as diminishing physiological instability.

In terms of actual biological models of panic disorder, the dominant theory has involved central nervous system noradrenergic dysregulation (Redmond, 1979). Effective drugs such as TCAs have been thought to inhibit firing of the locus coeruleus through stimulation of presynaptic α_2-autoreceptors, or through down-regulation of noradrenergic systems following chronic treatment (Heninger & Charney, 1988).

This model is compatible with the efficacy of TCAs and even of MAOIs in panic disorders. It is more difficult, however, to explain the beneficial effects of selective 5-HT re-uptake blockers (see below). While this class of drugs could help panic disorder via the influence of serotonergic projections from pontine and midbrain raphe nuclei onto noradrenergic nuclei such as the locus coeruleus (Gorman *et al*, 1989), their efficacy may also be due to primary dysregulation of serotonergic neural systems in panic disorder. This point is discussed further below.

Monoamine oxidase inhibitors

Open trials with iproniazid (West & Dally, 1959; Sargant, 1961) suggested that the MAOIs were efficacious for phobic anxiety, while Kelly *et al* (1970) first reported the efficacy of MAOIs (phenelzine) in patients with panic disorder. Sheehan *et al* (1980) found both phenelzine, 45 mg/day and imipramine, 150 mg/day to be superior to placebo in patients with 'endogenous anxiety' who suffered panic attacks. There was a slight advantage for the MAOI in reducing social disability, severity of symptoms, and phobic avoidance at the end of 12 weeks of treatment. Phenelzine, 45–90 mg/day (mean 55 mg/day) was highly effective in blocking panic attacks in a recent open trial of 35 patients with panic disorders (Buigues & Vallejo, 1987).

Phenelzine has been found to be superior to imipramine in atypical depressives with panic attacks (Liebowitz *et al*, 1988*c*), and to amitriptyline in outpatients having non-melancholic major depression with panic features (Robinson *et al*, 1985). While these data could be interpreted to show a broader patholytic effect for the MAOI, in both studies, identically depressed individuals without concomitant panic attacks failed to show superior responses to MAOIs.

However, MAOIs do appear to have a broader therapeutic range than TCAs. Several recent open (Liebowitz *et al*, 1986; Versiani *et al*, 1988) and controlled (Liebowitz *et al*, 1988*b*) trials found MAOIs to be effective in social phobia, where patients become severely anxious only when faced with possible scrutiny or evaluation by others. While formal studies are lacking, clinically, TCAs seem less useful for social phobia. Both atypical depressives and social phobics show high levels of interpersonal sensitivity, defined as an exaggerated concern with, and vulnerability to, negative responses from other people. In studies of atypical depression (Liebowitz *et al*, 1988*c*), social phobia (Liebowitz *et al*, 1988*b*), and hysteroid dysphoria (Liebowitz & Klein, 1981), phenelzine seemed particularly effective in reducing this trait.

Thus, MAOIs have a broad patholytic effect in depressive, anxiety, and phobic states, although studies in generalised anxiety disorder remain to be done. This may give them an advantage over other treatments in panic disorders. Nevertheless, because of the risk of hypertensive reactions with standard MAOIs, phenelzine is generally considered clinically as a back-up treatment, reserved for patients with panic disorders who respond insufficiently to TCAs. Descriptions of three patients who failed to benefit from adequate imipramine trials (Aronson, 1987) suggest that MAOIs may be useful in patients with panic disorders who have not responded to TCAs: two were borderline, and one was a very phobic patient whose panic attacks were fully blocked but who remained highly avoidant. In the light of phenelzine's possible superiority in treating phobic avoidance and atypical depressives, many of whom also meet criteria for borderline personality disorder (Liebowitz & Klein, 1981), phenelzine would be a reasonable next approach for these patients. Overall, while imipramine remains a standard anti-panic drug, phenelzine may be more useful for panic disorder patients with associated atypical depression, social phobia, borderline features, or resistant phobic avoidance.

The mechanisms by which MAOIs exert their patholytic effects are unclear. Because they have greater effects than TCAs on central nervous system dopaminergic activity, we have suggested a link between this neurotransmitter system and MAOI effects in social phobia and atypical depression (Liebowitz *et al*, 1987). However, Versiani *et al* (1989) have recently found the reversible MAO-A inhibitor, moclobemide, to have an efficacy comparable to that of phenelzine in social phobia. Moclobemide is thought to have noradrenergic but not dopaminergic effects (Stefanis *et al*, 1988). If so, greater efficacy might have been predicted for moclobemide in endogenous depression and panic disorders than in social phobia or atypical depression. Simultaneous clinical and biochemical studies of moclobemide in panic disorders, social phobia, and atypical depression could thus be very illuminating.

Serotonin re-uptake blockers

Several studies suggest that drugs which selectively affect serotonergic transmission may have efficacy in panic disorders. Kahn & Westerberg (1985) reported the 5-HT precursor 5-hydroxytryptophan (5-HTP) to have anti-panic properties. This finding was replicated in a controlled study (Kahn *et al*, 1987) in which 5-HTP reduced anxiety symptoms in comparison to placebo, but was less effective than clomipramine. Zimelidine, a potent selective 5-HT re-uptake inhibitor, was effective in agoraphobia with panic attacks in two open trials (Evans & Moore, 1981; Kockzkas & Weldin, 1981), and in one double-blind, placebo-controlled study (Evans *et al*, 1986).

Fluvoxamine, another selective 5-HT re-uptake inhibitor, has recently been found to be equipotent to clomipramine in 50 patients with anxiety disorders (Den Boer *et al*, 1987). In another comparison (Den Boer & Westenberg, 1988), fluvoxamine was effective, while maprotiline – a noradrenaline re-uptake inhibitor – was ineffective in 44 patients who had panic disorder with agoraphobia; the maprotiline dose, however, may have been too low (see below). In a third comparison (Den Boer, 1988), fluvoxamine was effective and ritanserin – a specific 5-HT_2 receptor antagonist – was ineffective in a placebo-controlled study of 60 patients with panic disorder. Den Boer *et al* (1987) have also noted a biphasic response to treatment with both clomipramine and fluvoxamine, with panic symptoms initially worsening for 1–2 weeks before improving.

Fluoxetine is a selective 5-HT re-uptake blocker; in our first open pilot study, 16 patients were treated with doses ranging from 10–70 mg/day (Gorman *et al*, 1987): seven were responders and nine were non-responders. Eight of the nine non-responders, however, dropped out because of early adverse side-effects, mainly increased agitation, restlessness, jitteriness, diarrhoea, and insomnia. When initial dosages of 2.5–5 mg/day were employed in a subsequent sample of 25 patients with panic disorders, 20 showed marked to moderate improvement, such that their panic symptoms were substantially relieved or in complete remission (Schneier *et al*, unpublished data). These data suggest that patients with panic disorder are unusually sensitive to side-effects from fluoxetine, since 20 mg/day starting doses are routinely used in patients with depression or obsessive-compulsive disorders without difficulty. It seems likely that serotonin re-uptake blockers could become widely used in panic disorders, because they lack many of the problems associated with other forms of medication now employed.

Serotonergic inputs into the locus coeruleus provide an explanation for the efficacy of 5-HT re-uptake blockers in panic disorders which is compatible with the noradrenergic model described above. Nevertheless, they also raise the possibility that panic patients suffer some primary serotonergic dysregulation. Central serotonergic hypersensitivity in panic disorders was suggested by Kahn *et al* (1988), who found that a low oral dose of methchlorophenylpiperazine (MCPP) (0.25 mg/kg) resulted in selective induction of anxiety and elevation of cortisol in ten patients with panic disorders, as compared with 11 normal controls. However, Charney & Heninger have presented data contrary to this, citing the lack of differences between panic patients and controls in response to intravenous tryptophan (Charney & Heninger, 1986) or to intravenous MCPP (0.1 mg/kg) (Charney *et al*, 1987). Kahn & Van Praag (1988), argue, however, that tryptophan does not test post-synaptic 5-HT sensitivity (Van Praag *et al*, 1987), and that 0.1 mg/kg MCPP given intravenously may be too large a dose to detect supersensitivity in patients with panic disorders. The lack of efficacy of maprotiline, in comparison with fluvoxamine, for blocking panic attacks (Den Boer, 1988) also suggests serotonergic rather than noradrenergic mechanisms for anti-panic effects, although the maprotiline dosage used (up to 150 mg/day) may have been too low, and not equivalent to the fluvoxamine dosage (also up to 150 mg/day). The only other relatively selective noradrenergic agent studied in panic disorders is desipramine, and dosages of 200 mg/day or more of this were generally required for good clinical effects in an open trial (Lydiard, 1987).

Other antidepressants

In addition to maprotiline, two other antidepressants – bupropion and trazodone – have been reported to be ineffective in panic disorders. Sheehan *et al* (1983) found that bupropion was ineffective in reducing the frequency of panic in any of 13 patients with panic disorders, and attributed this to the drug's selective dopaminergic effects. Similarly, in comparison with imipramine or alprazolam, trazodone was ineffective for panic (Charney *et al*, 1986): this was cited as evidence for noradrenergic rather than serotonergic mediation of panic disorders, since trazodone has primarily 5-HT effects. Ten of the 27 patients assigned to trazodone terminated treatment prematurely, however, because of adverse effects such as increased anxiety, excessive sedation, lightheadedness, and nausea. These patients may have been exhibiting serotonergic hypersensitivity, since trazodone is relatively well tolerated by depressed patients. Further, the post-synaptic 5-HT agonist MCPP, is a principal metabolite of trazodone. MCPP has been found to be panicogenic in one challenge study of panic disorders (Kahn *et al*, 1988), and could exacerbate symptoms in patients with panic disorder who were given trazodone.

Personal practice

In terms of personal practice, I usually turn first to imipramine to treat panic disorders, since it is extensively tested and offers a favourable risk–benefit ratio. In panic disorder, it is important to start imipramine treatment with low doses (25 mg/day) and to warn patients that they may feel more jittery or anxious initially. If this occurs, the dose can be lowered to 10 mg/day.

The other TCAs offer no advantages over imipramine for panic disorders. An exception is the lower incidence of anticholinergic side-effects observed with desipramine, which I will turn to if needed. However, desipramine may make patients even more jittery than imipramine.

If anticholinergic or other side-effects such as weight gain pose a problem for panic disorder patients on TCAs, the use of fluoxetine should be considered, but it often has to be started in a low dosage such as 5 mg/day, because it initially can make panic patients feel very anxious and overstimulated. Another disadvantage of fluoxetine is that it must be stopped 4–5 weeks before an MAOI can be started.

High-potency benzodiazepines, such as alprazolam, are effective more quickly than the antidepressants, and should be used for patients who need immediate relief, either because of severe distress or an important forthcoming event. Usually, it is advisable to try to switch such patients to imipramine after some time. Alprazolam is often used in conjunction with an antidepressant for additional control of panic or anticipatory anxiety. Clonazepam can also be used, and sometimes gives better control than alprazolam because it is longer-acting. However, it can sometimes cause a lowering of mood, which does not seem to occur with alprazolam. No particular difficulty should be experienced in taking patients off these benzodiazepines, but a slow tapering off is required, and this may be easier with a longer-acting drug such as clonazepam.

MAOIs are utilised for the most refractory or difficult cases. They are the most potent agents available for resistant panic attacks, residual anticipatory anxiety, or phobic avoidance. Phenelzine is most frequently used in this regard.

Formal exposure therapy is reserved for patients who still have agoraphobic difficulties, despite adequate medication. When panic attacks are treated with medication, some patients are quickly able to resume their normal functioning, and others remain fearful and phobic. The latter must be closely studied to see if they still have residual panic attacks, in which case medication adjustment is indicated, or to see whether they are just fearful of having another panic attack, in which case exposure therapy may be helpful. Exposure therapy itself is unlikely to shorten the time for which medication must be taken, but perhaps the newer forms of cognitive behaviour therapy that focus on controlling panic symptoms as well as avoidance may prove helpful in this regard.

Discussion

Important remaining issues in this subject include the mechanisms of action of antidepressants in panic disorders, methods of interaction and sequencing of drugs with cognitive behavioural treatments, and the optimal duration of therapy to minimise relapse following the discontinuation of medication.

To date, however, the rapid and often dramatic efficacy of antidepressants in panic disorders has brought into treatment many patients, some of whom may have previously found psychotherapy unhelpful or unacceptable. It will therefore have enhanced the credibility of psychiatric care in the eyes of both patients and other medical specialists, broadened the applicability of the medical model of treatment for mental disorders, stimulated a number of useful pathophysiological hypotheses, and had a significant impact on the classification of anxiety disorder.

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Biochemical Aspects of the Pharmacology of Moclobemide

The Implications of Animal Studies

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Administration of moclobemide – a relatively short-acting, reversible inhibitor of monoamine oxidase-A (MAO-A) – to experimental animals potentiates the pressor responses to intravenously injected tyramine, but such effects are moderate, short-lived, and much less apparent when the tyramine is given orally. The ability of moclobemide to potentiate the pharmacological actions of amine substrates for MAO-A in *in vitro* preparations is very weak, unless the drug is 'activated' by prior incubation with the tissues. However, animal experiments, both *in vitro* and *in vivo*, can give realistic indications not only of the mode of action of inhibitors of MAO and any toxicity, but also, in the case of MAO inhibitors, of the chance of potentially life-threatening hypertensive crises following inadvertent ingestion of amine-containing food or medicaments. Animal tests may also reveal any influence MAOIs have on amines released from non-neuronal stores.

Whatever the trends underlying the development of treatment methods for depression, the need for safety in drug usage is paramount, not simply to ensure that drugs which may be used over periods of weeks or months have no unwanted toxic or carcinogenic activity, but also to exclude properties that either discourage compliance by patients or make it easy for them to take a fatal overdose. A further problem, which has greatly restricted the use of the classical monoamine oxidase inhibitors (MAOIs) is the possibility of unforeseen and potentially fatal interactions with certain constituents of the diet and with commonly used medicines.

The use of drugs that inhibit MAO (monoamine: O_2 oxidoreductase [deaminating], EC 1.4.3.4) in the treatment of depression dates back to the 1950s, when iproniazid was introduced (Crane, 1957; Kline, 1958). Biochemical studies of MAO have revealed that the enzyme is not a single entity: it comprises two very similar but separate enzymes – MAO-A and MAO-B – with different distributions between species and between tissues of the same species (see Tipton, 1986). The target enzyme in the treatment of depression appears to be predominantly MAO-A (Lipper *et al*, 1979).

However, the use of MAOIs as antidepressants has been marred by reports of toxicity associated particularly with hydrazine agents. More dramatic, though, have been the reports of sudden life-threatening hypertensive crises following the ingestion of food or drink containing sympathomimetic amines, of which tyramine is the most common. This was named the 'cheese effect' because some cheeses are rich sources of tyramine (Blackwell, 1963; Natoff, 1965; Blackwell *et al*, 1967; Da Prada *et al*, 1988*b*). Potentiation of the pressor actions of intraduodenally administered sympathomimetic amines such as tyramine and phenylethylamine by inhibition of MAO, emphasises the importance of the gut MAO in protecting the individual from dietary amines (Blackwell & Marley, 1966). Recent evidence (Callingham *et al*, 1985; Hasan *et al*, 1988) indicates that in rat gut at least, MAO-A is the predominant MAO activity. This, coupled with observations that MAO-A appears to be the exclusive activity in sympathetic vasomotor nerves (Jarrott & Iversen, 1971), suggests that it would be difficult to divorce the antidepressant action of MAOIs from a potential to cause the cheese effect. In addition, the traditional MAOIs have all been irreversible in their action, so that substantial inhibition of MAO in gut as well as in vasomotor neurones is inevitable. Recovery of enzyme activity is dependent on the synthesis of new enzyme at a speed governed solely by the rate constant of degradation of the enzyme, which may take days (Della Corte & Callingham, 1977; Della Corte & Tipton, 1980; Callingham *et al*, 1985).

However, due to the introduction of agents that are reversible competitive inhibitors of MAO-A, there has been a recent resurgence of interest in MAOIs as antidepressants. Thus, their effects can be expected to be concentration-dependent and opposed by an increase in substrate concentration such as would be seen e.g., following ingestion of amine-containing food or the unwise use of amine-containing 'cold cures'. The proviso would be that the drug was not present in an amount more than about three times its K_i value (Strolin Benedetti *et al*, 1983): above this concentration, potentiation of the pharmacological action of the amine substrate is likely. Such studies as those with the short-acting MAO-A inhibitor, CGP 11305A (brofaromine) (Bieck *et al*, 1983, 1984) illustrate the close correlation between pressor response and concentration of the inhibitor. The potential danger resulting from individual differences in pharmacokinetics could perhaps be reduced if the inhibitor were concentrated within the target organ by some appropriate uptake pump (Ross, 1987). Mechanisms such as these could then leave the MAO-A of gut and peripheral nerve largely unaffected, while achieving adequate antidepressant concentrations within the central nervous system (see Callingham & Ovens, 1988). Thus, the specifications of a safe and effective MAOI can be drawn up; all that remains is to make a compound that fits.

Biochemical properties of moclobemide

Of the several drugs that meet some, at least, of the above criteria, moclobemide (*p*-chloro-*N*-[2-morpholino-ethyl] benzamide, Ro 11-1163) is one of the most promising, though at the same time one of the most mysterious (Da Prada *et al*, 1982, 1983, 1984). At first sight, it appears to be a selective, reversible, but not very potent inhibitor of MAO-A, such that it would be difficult to attribute its antidepressant action exclusively to inhibition of MAO-A in the brain.

Figure 1 illustrates the repeated observation that moclobemide (*in vitro*) is a very poor MAOI even with 5-hydroxytryptamine (5-HT), which is almost exclusively a substrate in the rat liver for MAO-A (see Fowler *et al*, 1978). However, this experiment was performed without any pre-incubation of inhibitor with liver homogenate before the addition of substrate, since this should not be necessary if moclobemide is truly competitive in nature. If pre-incubation is employed, a substantial increase in potency is seen (Fig. 2), together with obvious deviations of the regressions obtained in the presence of the higher concentrations of moclobemide.

Experiments such as these suggest that even *in vitro*, moclobemide may be converted to a more active form (Da Prada *et al*, 1982, 1983, 1984). However, there has been doubt as to whether or not the inhibition of MAO-A is entirely competitive or, if it is not, if it is completely reversible. Figures 1, 2 and 3 are in the form of Hanes-Woolf plots, where competitive inhibition is represented by an upward parallel displacement of the regression. In Fig. 2, the parallel shift is not maintained after pre-incubation for 60 min, indicating the presence of a non-competitive component. Other evidence from pre-incubation experiments is even stronger in suggesting that the inhibition becomes mixed or even non-competitive (Da Prada *et al*, 1989). In this respect, moclobemide is clearly different from the potent, selective, competitive inhibitor of MAO-A, cimoxatone, with a K_i value of 3.5 nmol, which always yields

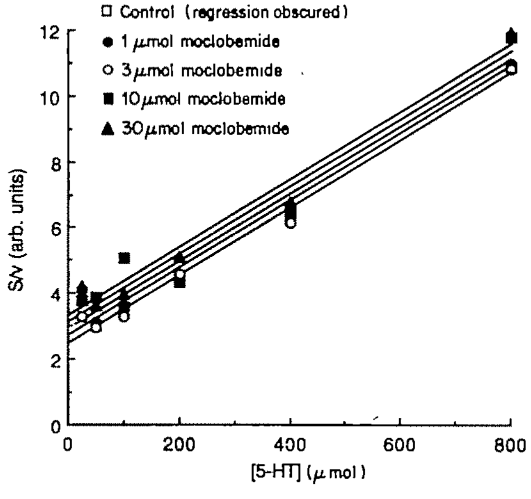

FIG. 1 A Hanes-Woolf plot of the effect of moclobemide on the deamination of 5-HT by MAO-A of rat liver homogenate without pre-incubation of enzyme and inhibitor before the addition of substrate.

Abscissa: 5-HT concentration (S), ordinate: S/velocity of reaction in arbitrary units. The points are means of three determinations of enzyme activity following incubation for 5 min at 37°C of tritium-labelled substrate and homogenate under an atmosphere of oxygen. Radioactive deamination products were extracted by organic solvent as described by Callingham & Laverty (1973) with the exception that the benzene used in the original method was replaced with toluene. Radioactivity was counted in a Packard 2000CA liquid scintillation spectrometer with automatic external standardisation. Control experiments indicated that a 5 min incubation period was on the linear part of the enzyme-time progress curve. No deviation from parallel was found between any of the regression lines.

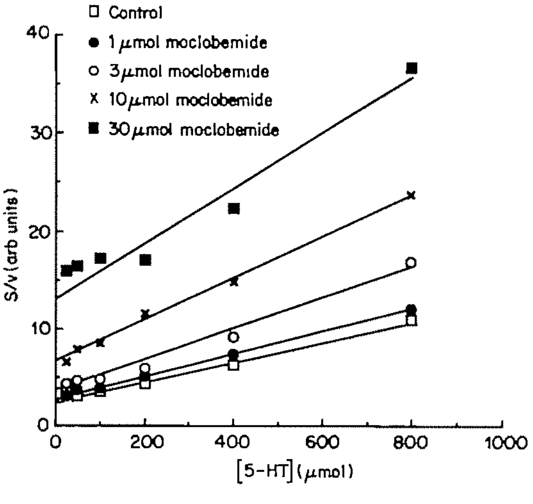

FIG. 2 A Hanes-Woolf plot of the effect of moclobemide on the deamination of 5-HT by MAO-A of rat liver homogenate following pre-incubation of enzyme and inhibitor for 60 min, before the addition of substrate.

Abscissa: 5-HT concentration (S), ordinate: S/velocity of reaction in arbitrary units. The points are means of three determinations of enzyme activity following incubation for 5 min at 37°C of tritium-labelled substrate and homogenate under an atmosphere of oxygen after the initial pre-incubation period. All other experimental details are as described in Fig. 1. Especially at the higher concentrations of moclobemide, deviations from parallel are obvious. This indicates the presence of a non-competitive component of the inhibition that has developed during the period of pre-incubation.

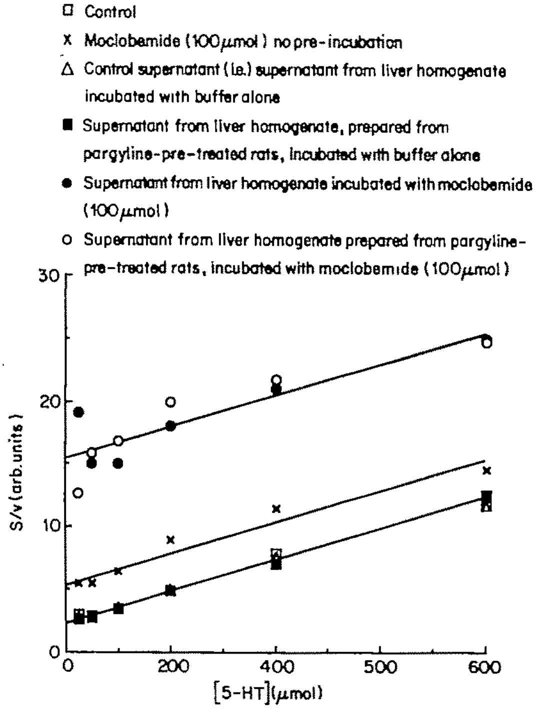

FIG. 3 A Hanes-Woolf plot of the effect of supernatant fractions obtained by incubating moclobemide (100 μmol) with a crude homogenate (1:10 w/v) of rat liver for 60 min on the deamination of 5-HT by rat liver MAO-A.

Abscissa: 5-HT concentration (S), ordinate: S/velocity of reaction in arbitrary units. The preparation of the supernatant fractions is described in the text. The points are means of three determinations of enzyme activity against 5-HT. All other experimental details are as described in Fig. 1. Pretreatment of the rats with pargyline does not prevent the increase in potency seen following incubation with liver homogenates.

parallel regressions in experiments of this nature, whether pre-incubation is used or not (Strolin Benedetti *et al*, 1979; Fowler & Strolin Benedetti, 1983). Amiflamine has also been shown *in vitro* to be fully reversible (Ask *et al*, 1982, 1984).

The increase in the magnitude of the MAO-A inhibition following addition of moclobemide, pre-incubated separately, is shown in Fig. 3. In this experiment, 8 × 10^{-4} M moclobemide was incubated at 37°C with an equal volume of a crude homogenate of rat liver (1/10 w/v) for 60 min. The mixture was then centrifuged at 120 000 × *g* for 60 min to produce a supernatant containing moclobemide together with an unknown quantity of its supposedly active metabolite or metabolites. An identical incubation was also performed, but with a liver homogenate from rats pre-treated with 30 mg/kg pargyline hydrochloride (two intraperitoneal injections 18 and 3 h before killing) to inhibit irreversibly all MAO-A and MAO-B in the liver. Control experiments showed that no pargyline was carried over in the supernatant. The supernatant fractions were stored at −20°C until used; the MAO-inhibiting activity remained stable for many weeks. Aliquots were then added to normal homogenates of rat liver, and the MAO activity measured radiochemically by a method slightly modified from that described earlier (Callingham & Laverty, 1973). It is noteworthy that under these conditions, deviations from parallel had apparently disappeared – an effect previously seen but hardly noticed (Callingham & Ovens, 1988). This may also be relevant to results suggesting that the putative active metabolites of moclobemide may be short-lived (Da Prada *et al*, 1988*a*).

The purpose of this experiment was two-fold. Firstly, to demonstrate that the nature of the inhibition of MAO-A activity brought about by moclobemide changed with pre-incubation, and secondly, to resolve an uncertainty generated by our own earlier work. Some time ago, we had suggested that the activity responsible for the conversion of moclobemide could be MAO itself (Burton *et al*, 1984). This was based on the observation that pre-incubation of moclobemide with homogenates of livers taken from pargyline-treated rats did not appear to give rise to any increase in potency of MAO-A inhibition, when measured with 1 mmol 5-HT (Burton *et al*, 1984). Subsequently, we were unable to confirm these results when we used a full kinetic analysis over a range of 5-HT concentrations with homogenates of liver, brain, or vas deferens of the rat, and supernatant samples from both normal and pargyline-treated rats (Callingham & Ovens, 1988). Figure 3 shows that pargyline does not influence the formation of active metabolite, and illustrates the need to undertake a full kinetic analysis, rather than rely on a single substrate concentration.

For an enzyme inhibitor to be truly competitive, it is imperative that it should be fully and rapidly reversible. While there were indications that, when pre-incubated *in vitro* before addition of substrate, the inhibition of MAO-A was readily reversible (Burton *et al*, 1984), attempts to reverse the inhibition of MAO in tissues taken from animals pre-treated with either moclobemide or brofaromine by dilution or by dialysis were largely unsuccessful (Waldmeier *et al*, 1983; Waldmeier, 1985). Moreover, the picture has been complicated further by the observation that a metabolite of moclobemide, Ro 16-6491, is a potent reversible inhibitor of MAO-B (Da Prada *et al*, 1986).

In an attempt to resolve some of these uncertainties, Keller *et al* (1987) studied the inhibition of MAO *ex vivo* (i.e. where the inhibitor is given to animals at various times before they are killed and their organs removed for assay of MAO activity) in rat brain and liver by moclobemide, and compared its effects with those of brofaromine as well as with those of the MAO-B inhibitors, almoxatone and Ro 16-6491 (Kettler *et al*, 1985; Da Prada *et al*, 1986). An oral dose of moclobemide (300 μmol/kg), given 2 h before decapitation, resulted in a reduction of MAO-A activity in liver homogenates to about 15% of control value. Dialysis of the homogenates at 37°C caused complete recovery of MAO-A activity, but this was not seen when dialysis was carried out at 13°C, and when brofaromine (30 μmol/kg) replaced moclobemide, only slight recovery was seen. With moclobemide, partial recovery, at 37°C but not at 13°C, was seen when homogenates of brain were made in Krebs-Ringer buffer, but almost complete recovery was seen with homogenates made in distilled water. Recovery of MAO-B inhibition after Ro 16-6941 was rapid and complete at both temperatures, but not after almoxatone. Control experiments with the irreversible MAOIs, clorgyline and selegiline (for MAO-A and MAO-B respectively), showed no recovery from inhibition. It would appear, therefore, that whatever the nature of the active metabolite, there is little or no evidence for covalent binding between inhibitor and enzyme. Such an interaction is typical of the 'suicide inhibitors' (suicide substrates, K_{cat} or mechanism based inhibitors), i.e. agents which look to the enzyme like genuine substrates but which undergo conversion by the enzyme to a highly reactive product that binds covalently as a powerful inhibitor (see Da Prada *et al*, 1988*a*).

Further analysis of the time dependency of the inhibition of MAO by moclobemide has revealed more intriguing effects (Da Prada *et al*, 1988*a*). Again, moclobemide was compared with brofaromine and with Ro 16-6941 and its more potent analogue, Ro 19-6397. While confirming both the increase in potency of moclobemide and of brofaromine as inhibitors of MAO-A and the conversion to non-competitive kinetics with incubation at 37°C, such effects were also seen with Ro 19-6327. In brain homogenates, the increase in potency of moclobemide was temperature-dependent following 2 h of incubation, with maximum potency achieved at 37°C. However, in liver homogenates incubated for the same period, increase in temperature appeared to reduce the formation of active metabolite. Da Prada *et al* (1988*a*) suggest that this may be the result of the high drug metabolising activity of the liver, which caused the metabolite to be broken down almost as quickly as it was formed. They conclude that, since in *ex vivo* studies (Keller *et al*, 1987) enzyme activity is rapidly restored at 37°C but not at low temperatures, this adds weight to the contention that moclobemide, once removed from the MAO active centre, is rapidly converted to an inactive metabolite. Although the kinetics are non-competitive after pre-incubation and appear to result from the formation of a mechanism-based inhibitor, the arrival of substrate in the vicinity leads to its rapid displacement and inactivation. Such a mode of action would be consistent with observations that the cheese reaction is much reduced in tests undertaken in human subjects (Korn *et al*, 1986, 1988). This recalls the observations that neostigmine and physostigmine, while alkylating the active centre of acetylcholinesterase, do so at such a low activation energy that they appear to be competitive inhibitors in most pharmacological tests. Are we seeing a similar phenomenon with moclobemide and MAO-A?

Animal pharmacology of moclobemide

Much animal pharmacology in this field will continue to be marked by the great attention that must be paid to testing for the cheese effect in animal models (see Callingham & Ovens, 1988). However, when the animal pharmacology of moclobemide is examined, it seems that, unlike powerful competitive MAO-A inhibitors such as cimoxatone, moclobemide has rather little effect on the pressor responses to indirectly-acting sympathomimetic amines. For example, Da Prada *et al* (1984) reported that it caused only minimal potentiation of the pressor responses in conscious rats, following oral administration of tyramine. While this is disappointing from the pharmacologists's point of view, it must be a reasonable supposition that the risk of the cheese effect will be less with moclobemide than that seen with the currently available MAOIs. Further exploration of this question may also result in something of the underlying physiology being revealed (see Callingham, 1986).

At least two important factors bear closely on the relevance of pharmacological studies undertaken in whole animals. The first is the chosen route of administration, since the clinical use of MAOIs involves oral administration, and unwanted interactions are usually with amines in the gastrointestinal tract. Studies in both animals and in human volunteers where the test amines are administered intravenously must inevitably measure the worst case, and the same could also be said about *in vitro* studies. Furthermore, it is important not only to measure the peak magnitude, but also the area under any response: there is much evidence that effects on duration are seen even when the peak height is virtually unchanged. Finberg & Youdim (1988) explored this aspect in conscious rats, where the effects of moclobemide, cimoxatone, amiflamine, and brofaromine were compared both with each other and with the effects of clorgyline on the pressor responses to intravenous injections of tyramine, 60 min following the intraperitoneal injection of the inhibitor. Much greater potentiations of the areas under the responses were seen than on peak height, with all MAOIs used. The severe bradycardia that occurred during the pressor rises reduced the height of the response following MAO inhibition, and provides clear evidence that to report only the potentiation in terms of the arterial blood pressure rise, substantially underestimates the effect. Treatment of some of the rats with atropine methyl nitrate (1 mg/kg) led to the bradycardia being converted to tachycardia; under these conditions, moclobemide (5 mg/kg) caused a substantial increase in the height of the pressor response to tyramine. These authors also showed that after 24 h, while the potentiating effect of the reversible MAOIs had disappeared, it was still present following clorgyline. Precise quantitative comparisons are, as these authors point out, difficult to do in this way, since although all inhibitors caused substantial inhibition of hepatic MAO, it is possible that the magnitude of the inhibition could be critical. If this is the case, the possibility that both effectiveness and the risk of the cheese reaction could be influenced by variations in individual pharmacokinetics cannot be ignored. How such differences would influence the therapeutic action of agents such as moclobemide, which may need 'activating', by conversion to a more active metabolite, is difficult to determine.

Pharmacological experiments on *in vitro* preparations, while being far removed from the patient, do have the advantage that the conditions can usually be controlled. For example, the isolated vas deferens of the rat has been used to show potentiation of the tension responses to sympathomimetic amines in the presence of MAOIs (Finberg *et al*, 1981; Finberg & Tenne, 1982; Youdim & Finberg, 1983). The rat anococcygeus muscle (Gillespie, 1972, 1979) is particularly useful because of its relatively simple innervation, with little contribution from preganglionic fibres. The isolated perfused mesenteric arterial bed of the rat (McGregor, 1965) can be employed successfully, as can several other *in vitro* preparations (see Callingham, 1986): we have used the anococcygeus muscle to examine the actions of MAOIs (Callingham & McCarry, 1984; Callingham, 1986). Without pre-incubation, even at concentrations of moclobemide as high as 100 μmol, potentiation of the responses to a range of sympathomimetic amines, including noradrenaline, dopamine, phenylethylamine, and tyramine, was very small (McCarry *et al*, 1987). However, if the moclobemide was pre-incubated with liver homogenates as described above, potentiations could then be revealed, especially in the areas under the responses (Callingham & Ovens, 1988). It is important, though, that under the conditions of these experiments, other properties of MAOIs may be relevant, including actions on neuronal uptake of amines or on receptors. For example, moclobemide has been shown by ligand-binding studies to have a weak but measurable affinity (K_i value of about 10 μmol) for both α_1- and α_2-adrenoceptors.

Much attention has been given recently to the study of MAO inhibition on responses to mainly indirectly acting sympathomimetic amines, typified by tyramine. However, an amine that should be considered here is 5-HT, especially as it is almost invariably used in biochemical tests as a substrate for MAO-A; its pharmacological actions in the periphery tend to be neglected. We have turned our attention to *in vitro* preparations of blood vessels of the rabbit, because they contain substantial amounts of MAO-B activity, which may exceed that of MAO-A. It was felt that these tissues would more closely represent others where MAO-A was not the sole MAO activity, and thus would more resemble a general case.

Method

The specific activities of the amine oxidase activities in the aortas of the rabbits used in our studies (see below) were approximately: 59, 172, and 105 nmol/h/mg protein content for MAO-A (400 μmol 5-HT), MAO-B (400 μmol benzylamine) and SSAO (semicarbazide-sensitive amine oxidase, 10 μmol benzylamine), respectively (uncorrected for extraction efficiency).

Male New Zealand white rabbits (1.2–2 kg) were killed by a blow to the head, followed by exsanguination. The thoracic aorta was dissected free of connective tissue and placed in ice-cold physiological saline (modified Krebs-Henseleit), gassed with 95% O_2 and 5% CO_2. Segments of aorta (2 mm) were cut and mounted in organ baths at 37°C between two rigid stainless steel wires, the upper of which was attached to a Grass Instruments FT-03 force transducer. The transducer output was amplified and recorded with a Grass Model 79D Polygraph via 7P1 DC pre-amplifiers. The resting tension chosen for these experiments was 2 g. After an initial equilibration period of 45 min, noradrenaline (1 μmol) was added to the bath. At the height of the contraction and before washing out the noradrenaline, acetylcholine (1 μmol) was added. A rapid relaxation was an indication that the segments were in good condition and still contained a functional endothelium (Figs 4 and 5).

Results

Figure 4 illustrates an attempt to discover whether or not a high concentration (100 μmol) of moclobemide could potentiate the responses to 5-HT. Exposure of the aortic segments to moclobemide, 10 min prior to the addition of 5-HT, caused no significant potentiation of the peak tension response. Furthermore, since 5-HT is a substrate for MAO-B in some tissues such as the human platelet (see Fowler *et al*, 1978), selegiline (L-deprenyl) was applied to the segments from 10—60 min before the addition of 5-HT. No potentiation was seen. Indeed, in some experiments (not shown), selegiline depressed the response, even though substantial amounts of MAO-B were present. Evidence of this nature would suggest

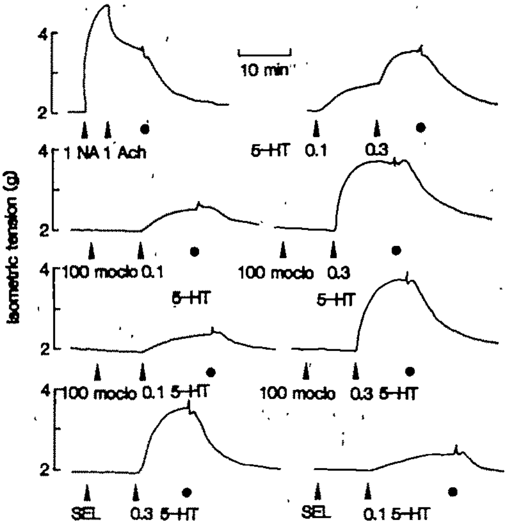

FIG. 4 Effect of moclobemide on the isometric tension responses of rabbit thoracic aorta to applied 5-HT.

Moclobemide (100 μmol) was added 10 min before the addition of either 0.1 or 0.3 μmol of 5-HT. Drugs were administered at the arrows and the organ bath washed out at ●. All concentrations are in μmol. NA: noradrenaline, Ach: acetylcholine, SEL: selegiline (0.3 μmol) added 10 min before 5-HT and then maintained in the bath to achieve irreversible inhibition of MAO-B. The resting tension on the aortic segments was maintained at 2 g. The apparatus used is described in the text. No obvious potentiation of the responses to 5-HT were seen.

that conversion of moclobemide to metabolites, such as Ro 16-6491, that inhibit MAO-B is not involved in the increase in potency on pre-incubation. However, this does not rule out the possibility that such a conversion may influence the actions of sympathomimetic amines that are inactivated by MAO-B.

The picture was not the same when the aortic segments were exposed to aliquots of the supernatant fractions from incubation of moclobemide and rat liver homogenates, as described above (Fig. 5). As with the biochemical experiments, quantitative results were difficult to obtain, since it is impossible to estimate the amount of the 'active' metabolite in the supernatant fraction, if indeed one really exists. However, exposure to a volume of supernatant that corresponds to 4 μmol (instead of 100 μmol) of moclobemide caused obvious potentiation of the responses to both 0.1 and 0.3 μmol 5-HT. This concentration of 'activated' moclobemide was the same as the approximate IC_{50} value of 'activated' moclobemide against the deamination of 5-HT by MAO-A in homogenates of rat anococcygeus muscle (McCarry *et al*, 1987). Similar results have also been obtained with rabbit pulmonary and iliac arteries.

Discussion

Whilst it is extremely difficult to make predictions from preliminary results such as these, they do serve to demonstrate that agents such as moclobemide could influence smooth muscle responses to 5-HT. If the same effects are seen in bronchiolar smooth muscle, they could have implications for the use of such compounds in asthma or other conditions where 5-HT and similar amines interact with smooth muscle-containing organs.

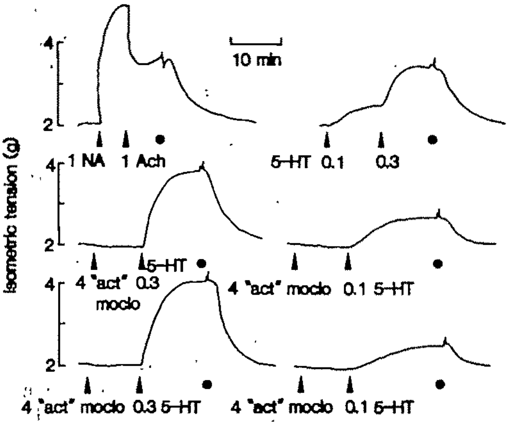

FIG. 5 Effect of supernatant fractions from the incubation of moclobemide with homogenates of rat liver on the isometric tension responses of rabbit thoracic aorta to applied 5-HT.

'Activated' moclobemide ('act' moclo), corresponding to 4 μmol of original drug was added 10 min before the addition of either 0.1 or 0.3 μM of 5-HT. Drugs were administered at the arrows and the organ bath washed out at ●. All concentrations are in μmol. NA: noradrenaline, Ach: acetylcholine. The resting tension on the aortic segments was maintained at 2 g. The apparatus used is described in the text. 'Activated' moclobemide at a concentration corresponding to 1/25th of that used without incubation caused substantial potentiation. Control experiments with the other supernatant fractions had no effect other than that from pargyline-treated rats, which also potentiated.

It is now clear that the effectiveness of moclobemide as an inhibitor of MAO-A is time-dependent and reversible, but the exact nature of the underlying mechanisms and the identity of the active form of the drug are still to be resolved. There is no doubt that potentiation of pressor effects of sympathomimetic amines can be brought about by moclobemide, as well as by all other MAOIs tested, and this is not surprising since, in experimental studies and especially *in vitro*, conditions can be so manipulated as to make a cheese effect inevitable. There is thus a need for a sound predictive test to be developed, and until that happens, differences in experimental methods may confound otherwise reliable data. Whether or not the production of metabolites that inhibit MAO-B is important for the use of moclobemide as an antidepressant cannot as yet be resolved experimentally. Indeed, recent and very detailed studies of the biochemical pharmacology of moclobemide (Burkard *et al*, 1989; Da Prada *et al*, 1989) provide convincing evidence in support of the view that MAO inhibition resides overwhelmingly in moclobemide itself and in its less potent *N*-oxide metabolite. In these circumstances, extrapolation from rat to man is a risky business, but perhaps not so risky as individual differences in pharmacokinetics and patient compliance.

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Effect of a Reversible Monoamine Oxidase-A Inhibitor (Moclobemide) on Sleep of Depressed Patients

J. M. MONTI

The effect of moclobemide, a short-acting, reversible, preferential monoamine oxidase-A inhibitor in a 4-week therapeutic trial, on the sleep of ten depressed patients, was assessed by polysomnographic recordings. Compared with their time on placebo, patients receiving moclobemide showed improved sleep continuity, particularly during the intermediate and late stages of drug administration. The total increase in sleep time was comprised of larger amounts of stage 2 non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Withdrawal of moclobemide was followed by a further increase of REM sleep, although values did not surpass those sometimes observed in adults with normal sleep. In these patients, the symptoms of depression were rated as being significantly improved during the study period.

The most predictable sleep abnormalities of endogenous depression consist of changes in wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Gold *et al*, 1988). They include: prolonged sleep latency, increased wakefulness, and early morning awakening; diminished slow wave sleep (stages 3 and 4); as well as short REM sleep latency and redistribution of REM sleep to the first half of the night (Gillin *et al*, 1984; Reynolds & Kupfer, 1987).

Many tricyclic, heterocyclic and monoamine oxidase inhibitor (MAOI) antidepressants suppress REM sleep and on discontinuation produce a significant rebound of REM sleep which can persist for many days or weeks. In some studies, onset of clinical improvement coincided with the attainment of total REM sleep suppression, which led to the suggestion that restoration of normal mood was dependent on the abolition of REM sleep (Vogel *et al*, 1980) or at least that this was a good predictor of clinical response (Dunleavy & Oswald, 1973; Passouant *et al*, 1973; Gillin *et al*, 1978; Kupfer *et al*, 1983). In contrast, trimipramine and amineptine increase REM sleep during chronic treatment (Di Perri *et al*, 1986; Wiegand *et al*, 1986).

The benzamide derivative moclobemide is a short-acting (half-life = 1 h), reversible, and selective brain monoamine oxidase-A (MAO-A) inhibitor (Da Prada *et al*, 1988). In contrast to the non-selective and irreversible MAOIs, moclobemide is devoid of hepatic toxicity, as well as having a very low liability to increase the pressor effect of dietary tyramine, so that strict diet restrictions may not be necessary (Amrein *et al*, 1988).

The aim of the present study was to determine the effects of moclobemide on sleep in patients with a depressive syndrome.

Method

Patients

Ten patients (three male, seven female), of mean age 44 ± 12 years, were included in the study. Their diagnoses (DSM-III) were: unipolar manic-depressive psychosis (six), major depressive disorder (three), and atypical depression (one).

All previous medication was withdrawn, 7–10 days prior to the study, and replaced by placebo. All patients and their relatives were informed about the objectives of the investigation, and gave their consent to participation.

Investigation

Polysomnographic sleep recordings were performed during the initial, intermediate, and late stages of treatment with moclobemide.

The period of investigation was 35 days, of which 16 were spent in the sleep laboratory. The first night was for the patient's adaptation to the laboratory; on the succeeding three nights, coinciding with the days on which placebo was taken, sleep was recorded and quantified, to estimate the extent and nature of sleep disturbance prior to treatment. On days 5–32, patients took moclobemide during the day. The initial dose was 150 mg daily, but this was then increased rapidly, so that by day 7, the maximum of 300 mg was being received, taken in three divided doses (08.00, 13.00 and 18.00 hours). The 300 mg dose was maintained from day 5 until day 32, so that patients received moclobemide for 28 days. During the investigation, patients came to the laboratory for nights 5–7 (initial stage of treatment), 18–20 (intermediate stage), and 30–32 (late stage). On the intervening nights, they slept at home. On the three days (33–35) following cessation of treatment, the patients received placebo, so that the effects of withdrawal of moclobemide on sleep could be observed.

Patients were interviewed by the psychiatrist during the first day of the baseline period, on treatment days 3, 7, 14, 21 and

28, and during the last day of the withdrawal period. The clinical consultation included administration of the Hamilton Rating Scale for Depression (HRSD) and Beck rating scale, as well as a self-evaluated rating scale.

On the nights when the patients attended the sleep laboratory, polygraphic sleep recordings were carried out over 8 h, using frontal, parietal, and occipital EEG leads, right and left electro-oculograms, chin electromyogram, ECG, and impedance thoracic electroplethysmography.

The sleep records were coded and scored blind. The variables scored were as follows:

(a) onset latency for NREM sleep (NREM sleep, from lights out to the appearance of the first spindle);
(b) total time awake;
(c) time awake after the onset of sleep;
(d) number of awakenings;
(e) total duration of sleep and duration of stages 1, 2, 3, and 4 NREM sleep;
(f) duration of REM sleep in minutes and as a percentage of total sleep time;
(g) REM latency (from the first spindle to REM sleep onset).

Data analysis

The mean value of each variable for placebo baseline, initial, intermediate, and late drug administration, and placebo withdrawal nights was tested for significance, using a one-way ANOVA, followed by comparison with placebo using the Scheffé test. The Kruskal-Wallis ANOVA by ranks was used to test whether any of the following were related to treatment: scores for clinical impression of severity of depression, HRSD and Beck rating scale, self-evaluation rating scale, or blood pressure fluctuations. When appropriate, the statistical significance of differences was assessed by the Wilcoxon matched pairs test.

Effect of moclobemide on sleep variables

Sleep was disturbed in all patients prior to treatment. During the placebo baseline period, latency to NREMS averaged 84.2 min, while in the period of moclobemide administration, there was a non-significant reduction of this value to a mean of 48.3 min. Total baseline time awake was 192.4 min, while time awake after the onset of sleep was 116.4 min — both of which were significantly reduced during moclobemide administration and in the withdrawal phase (Figs 1 and 2). These were accompanied by an increase in total sleep time (Fig. 3) from an average of 287.6 min during baseline to a mean of 345.2 min during the drug administration period.

During moclobemide administration, a significant increase in total NREM sleep was observed, which was maintained in the withdrawal period (Fig. 4); this was coupled with an increase in stage 2 (Fig. 5). With regard to slow wave sleep, stage 3 lasted only 2.2 min during the baseline period, and there was a slight, non-significant increase in this stage when patients were given moclobemide. Stage 4 was almost totally absent throughout the whole study period.

During the baseline period, the mean duration of REM sleep was 52.6 min (16.4% of total sleep time). On administration of moclobemide, REM sleep underwent a progressive increase,

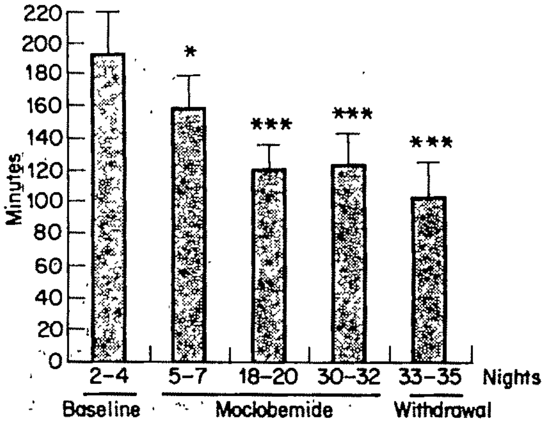

FIG. 1 Total wake-time. $*P<0.05$; $***P<0.001$.

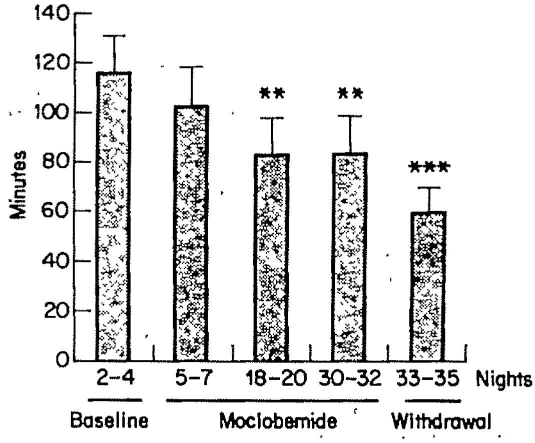

FIG. 2 Wake time after sleep onset. $**P<0.01$; $***P<0.001$.

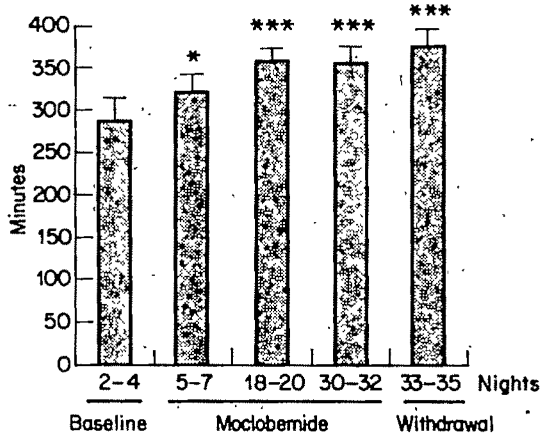

FIG. 3 Total duration of sleep. $*P<0.05$; $***P<0.001$.

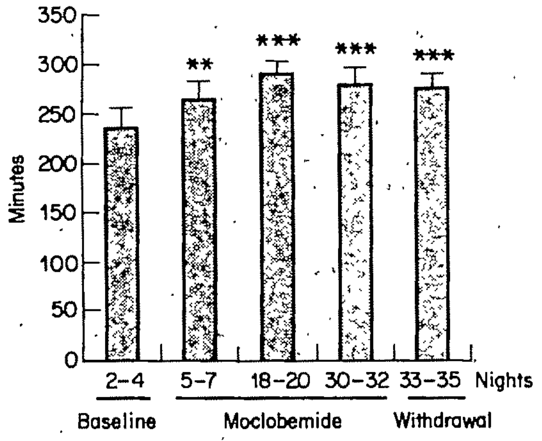

FIG. 4 NREM sleep time. $**P<0.01$; $***P<0.001$.

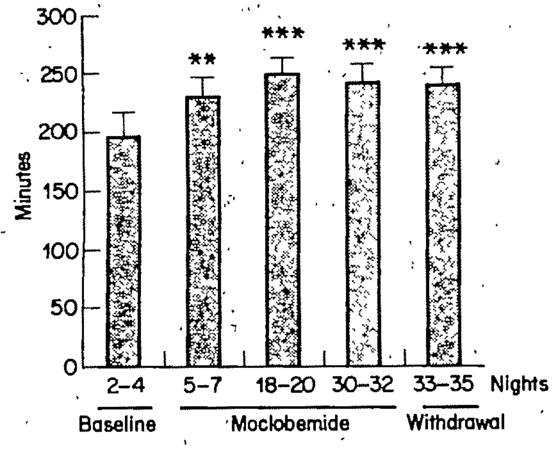

FIG. 5 Stage 2 non-REM sleep. $**P<0.01$; $***P<0.001$.

which became significant during the intermediate and late stages. During withdrawal, there was a further increase of REM sleep both in minutes and as a proportion of total sleep time, although the values did not surpass those observed in some adults with normal sleep (Figs 6 and 7). At baseline, mean REM sleep latency was 102.3 min; in five of the ten patients, the latency of the first REM period was short compared with healthy adult subjects, i.e. between 28 and 71 min. During moclobemide administration REM sleep latency was significantly increased, and significantly decreased on moclobemide withdrawal (Fig. 8).

Antidepressant effect

The efficacy of treatment was assessed by clinical impression as — very good in two patients, good in four, and moderate in four. Moclobemide was very well tolerated in eight patients, well in one and moderately well in one, patient each. The

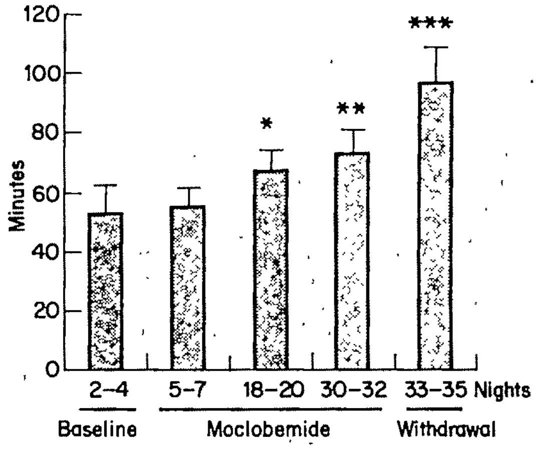

FIG. 6 REM sleep time in min. $*P<0.05$; $**P<0.01$; $***P<0.001$.

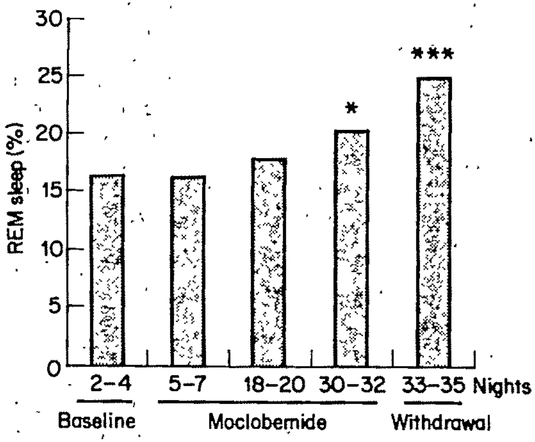

FIG. 7 REM sleep as percentage of total sleep time. $*P<0.05$; $***P<0.001$

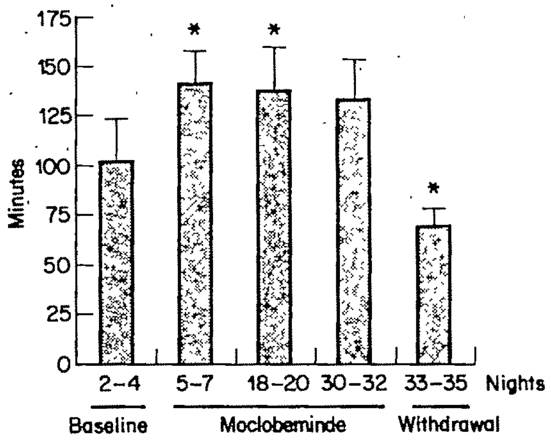

FIG. 8 REM sleep latency. $*P<0.05$.

antidepressant effect appeared between the third and the fifth days, reaching a maximum at 10–23 days.

Analysis of the HRSD, Beck scale, and self-rating scale scores showed that there had been significant reductions in scores: at day 21, there was 58.4% reduction in the HRSD, 52.1% reduction in the Beck scale, and 49.5% decrease in the self-rating scale. Clinical impression thus confirmed a significant reduction in the severity of depression in the sample.

Neither systolic nor diastolic blood pressure (supine and standing) showed significant change during the administration of moclobemide. Blood, urine, and liver function tests showed no abnormal changes during treatment. Adverse events, which were all mild or moderate, included: a metallic taste in the mouth ($n = 1$), mild stomatitis ($n = 1$), blurred vision ($n = 1$), anxiety ($n = 1$), constipation ($n = 1$), headache ($n = 1$), urinary frequency ($n = 2$) and oedema of the lower extremities ($n = 1$).

Discussion

The irreversible MAOIs phenelzine and tranylcypromine abolish REM sleep and provoke an increase of as much as 250% above baseline on withdrawal (Le Gassicke *et al*, 1965; Akindele *et al*, 1970; Wyatt *et al*, 1971; Dunleavy & Oswald, 1973). In contrast, the antidepressant effect of moclobemide occurred despite the absence of a striking REM sleep suppressant effect. It could be argued that this difference between the drug's effects on mood and on REM sleep might be related to the selective blockade of MAO-A. However, cimoxatone — another selective and reversible MAO-A inhibitor — induces alterations in REM sleep which are similar to those of the older MAOIs (Hoff *et al*, 1986). Since moclobemide has a short plasma half-life, and the last dose in this study was taken at 18.00 hours, it is possible that the REM sleep suppressant effect had already disappeared by the time the patients arrived in the sleep laboratory. However, in the study by Steiger *et al* (1987), the last dose of the selective and short-acting MAO-A inhibitor, brofaromine, was taken at 12.00 hours, yet REM sleep was significantly reduced. An alternative possibility is that a mild direct REM suppressant effect was counteracted by the expected increase in REM sleep that normally occurs during recovery from depression.

Although the sample size was small, the direction of the data in this study appears to indicate that improvement in quality and architecture of sleep occurs concomitantly with improvement in symptoms of depression.

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The Pharmacology of Reversible Monoamine Oxidase Inhibitors

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and D. VRANESIC

The older monoamine oxidase inhibitors (MAOIs) are mechanism-based, irreversible inhibitors of MAO; most inhibit both the A and B forms of MAO. Several of the drugs are hydrazine derivatives which have non-specific effects other than MAO inhibition. These properties convey disadvantages, which may be seen as serious, though infrequent, adverse events — the 'cheese effect', hepatotoxicity, amphetamine-like activity, orthostatic hypotension and anticholinergic effects. New, reversible MAOIs stem from a variety of chemical classes and are more specific in their effects, with relatively rapid onset of action, direct relationship between plasma concentration and pharmacological effect, and no prolonged carry-over phenomena.

Mechanism-based monoamine oxidase inhibition

In a mechanism-based reaction, a relatively inert substrate is converted by a normal enzyme reaction to a highly reactive intermediate which inactivates the enzyme without prior release from the active site. Helmkamp *et al* (1968) first described an example of a mechanism-based enzyme activated inhibitor: coli bacilli enzymatically change a relatively inert 3-decanoyl thiolester into a highly reactive breakdown product, which then permanently blocks the respective enzyme by means of covalent binding to it.

The theoretical advantages of such irreversible enzyme inhibitors were emphasised, for instance, by Abeles & Maycock (1976), Murphy (1978), Silverman & Yamasaki (1984), Walsh (1984), and Silverman & Zieske (1985). These include the potential for extremely specific drugs, and the possibility of producing an effect by means of this mechanism only where the effect is desirable and necessary; a single dose of such a drug can lead to very long lasting and perhaps permanent effects.

Older MAOIs such as isocarboxazid and tranylcypromine belong to this category of mechanism-based irreversible MAOIs, whereas in contrast, all compounds which have come into clinical development within recent years inhibit MAO reversibly. There are a large number of both theoretical and therapeutic reasons to account for the new, reversible MAOIs being preferable in clinical practice.

Pharmacokinetics

With single-dose administration, the duration of action of the new reversible MAOIs such as moclobemide is limited to some hours, whereas that of the old compounds such as tranylcypromine lasts several days. This cannot be explained by differences in pharmacokinetic properties (Robinson & Kurtz, 1978; Schoerlin & Guentert, 1989). Following a single-dose administration, the shape of the plasma concentration time curves of moclobemide and tranylcypromine are similar (Fig. 1).

Both substances are rapidly absorbed, and the maximum concentration in the plasma is reached within 1 h. Elimination proceeds rapidly, the elimination half-life being approximately 2 h (Table I).

An elimination half-life of less than 3 h is also a characteristic of the old irreversible MAOIs. However, in contrast to the irreversible MAOIs, the pharmacokinetic properties of the reversible drugs vary within a broader range (Schoerlin & Guentert, 1989). Elimination half-lives of reversible MAOIs are: less than 3 h for moclobemide and toloxatone; 5–12 h for amiflamine; 9–16 h for cimoxatone; and 12–15 h for brofaromine. Binding to plasma protein is weak for amiflamine, moderate for moclobemide and toloxatone, and very strong for brofaromine and cimoxatone (Table II).

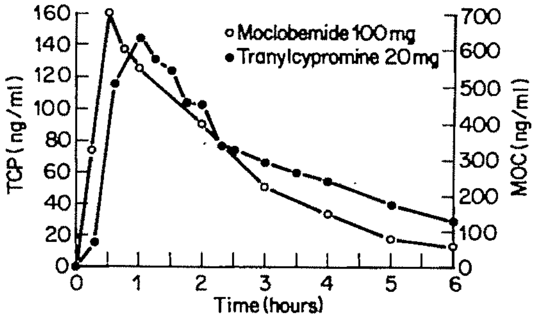

FIG. 1 Concentration profiles of moclobemide and tranylcypromine after oral dosing. TCP: tranylcypromine (Mallinger *et al*, 1986), MOC: moclobemide (data on file, F. Hoffmann-La Roche Ltd, Switzerland).

TABLE I

Comparative pharmacokinetics of tranylcypromine (10 mg) and moclobemide (150 mg) after single oral dosing (mean ± s.d.)

	Tranylcypromine[1]	*Moclobemide*[2]
t_{max} (h)	1:55 ± 0.99	1.02 ± 0.56
V_{beta} (litre/kg)	2:71 ± 1.29	1.79 ± 0.38
$t_{½}$ (h)	2.45 ± 0.57	2.04 ± 0.97
CL (ml/min/kg)	14:1 ± 10.30	11.80 ± 5.00
fm	> 0.95	>0.99

1. Mallinger *et al* (1986).
2. Data on file, F. Hoffmann-La Roche Ltd, Switzerland.

t_{max}: Time of maximum concentration.
V_{beta}: Volume of distribution during the terminal disposition phase.
$t_{½}$: Elimination half-life.
CL: Clearance.
fm: Fraction of dose metabolised.

TABLE II

Pharmacokinetic properties

	Protein binding (%)	*Volume of distribution (litre/kg)*	*Elimination half-life (h)*
Moclobemide	50	0.6–1.6	1.0–3.0
Toloxatone	50	1.1–1.6	0.9–2.5
Amiflamine	23	4.2–8.4	4.9–12.0
Cimoxatone	95	0.5–0.7	8.9–16.0
Brofaromine	98	4.3–6.0	12.0–15.0

Elimination of both reversible and irreversible MAOIs is almost exclusively by hepatic metabolism.

Binding kinetics

It has been known for several years that tranylcypromine is a mechanism-based irreversible MAOI (Paech *et al*, 1980; Silverman, 1983). The reaction kinetics were defined under *in vitro* conditions (Silverman & Zieske, 1985). Based on this *in vitro* reaction scheme and taking into account the synthesis of new enzyme molecules (Felner & Waldmeier, 1979), the time-course of MAO inhibition has been estimated by the use of an *in vivo* model (Fig. 2).

After oral administration, the concentrations of tranylcypromine at the site of action are assumed to equilibrate rapidly with those in plasma. Initially, tranylcypromine, as a relatively inert compound, is converted by a common enzymatic reaction to a highly reactive intermediate (E-I)″. This then interacts with two sites of the enzyme, the one leading to an irreversible (covalently bound) adduct (E-I)*, the other leading to a labile (reversible) adduct which rapidly decomposes to the enzyme (pathway (E-I)″ — E).

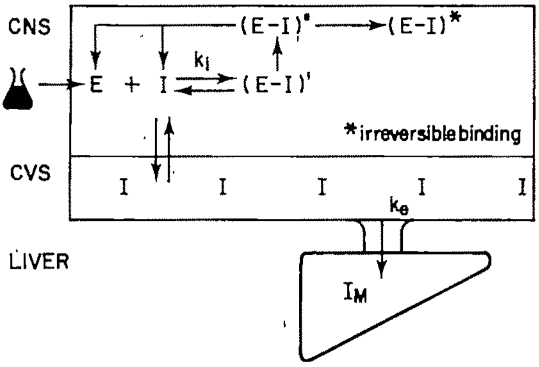

FIG. 2 Hypothetical model for the binding characteristics of tranylcypromine and MAO. E: enzyme (MAO), I: inhibitor (tranylcypromine), k_i: affinity, k_e: rate constant of elimination, CNS: central nervous system, CVS: blood, I_m: inhibitor metabolite(s).

Figure 3 illustrates the course of events during administration of tranylcypromine 10 mg t.i.d.

Since there is a lack of enzyme kinetic data in humans, the model calculations are tentatively based on *in vitro* parameters from rats and should be regarded accordingly. The model is not very sensitive to changes in model parameters and describes well the general pattern of MAO inhibition over time with tranylcypromine, as evaluated by tyramine pressor tests (Bieck & Antonin, 1982; Bieck *et al*, 1984).

After each ingestion, the maximum tranylcypromine concentration in the plasma is reached within 1–2 h. It then rapidly decreases, due to rapid metabolism by the liver, and there is hardly any accumulation. The required degree (> 70%) of enzyme inhibition is reached

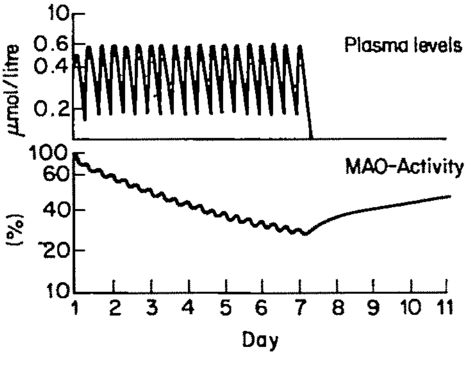

FIG. 3 Tranylcypromine (10 mg t.i.d.) plasma levels and MAO activity.

only slowly, steady-state levels of inhibition being attained after 1 week. After treatment is stopped, MAO remains inhibited for a long period, its activity only returning when MAO in sufficient quantity has been newly synthesised.

From this example, it is evident that the mechanism-based irreversible MAOIs have four definite disadvantages:

(a) Maximum biochemical effect is obtained only after many doses.
(b) There is difficulty in exerting control over efficacy by means of changing the dose or the dose interval.
(c) There are long-lasting carry-over effects.
(d) No direct relationship exists between pharmacokinetics and clinical effects.

For moclobemide, a mechanism-based inhibition of MAO has also been postulated, but — very importantly — inhibition is reversible (Burkard *et al*, 1989; Da Prada *et al*, 1989). The enzyme kinetic parameters for moclobemide are unknown, but experimental results (Koulu *et al*, 1989) show that following a single (200 mg) dose of moclobemide, MAO inhibition reaches 80% after 2 h. This time course of inhibition could be simulated by only slightly modifying the corresponding rate constants known for tranylcypromine. The hypothetical model is shown in Fig. 4.

After repeated administration, the bioavailability of moclobemide increases (Schoerlin *et al*, 1987), but its pharmacokinetic behaviour is otherwise similar to that of tranylcypromine, whereby rapid absorption is followed by rapid elimination. However, because of the reversibility of MAO inhibition, the similar shape of the plasma concentration time-course has fundamentally different consequences: moclobemide produces maximum MAO inhibition after the first dose. Inhibition lasts for a few hours; even though there is some accumulation during the first week of administration, inhibition already starts to decrease towards the end of the dosing (t.i.d.) interval, and disappears, i.e. MAO activity is completely reinstated within 24 h of the last dose of the schedule (Fig. 5). Calculations from this model indicate a slight overshooting of MAO-A activity (activity > 100%) which regains the 100% level only some days after termination of treatment (Fig. 5). This effect disappears if a lower synthesis rate of MAO-A is considered. It is likely that the synthesis rate in humans is much slower than in rats, and thus a MAO-A activity > 100% is not to be expected.

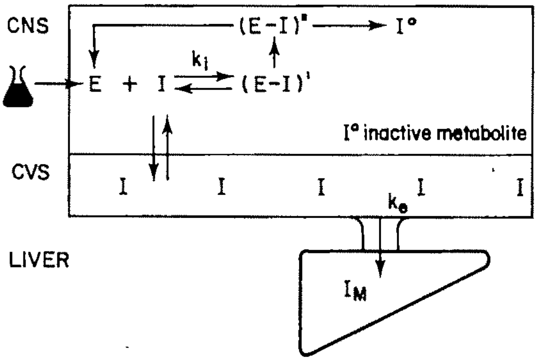

FIG. 4 Hypothetical model for the binding characteristics of moclobemide and MAO. E: enzyme (MAO), I: inhibitor (moclobemide), k_i: affinity, k_e: rate constant of elimination, CNS: central nervous system, CVS: blood, I_M: inhibitor metabolite(s).

The MAO inhibitory characteristics of moclobemide illustrate very distinct advantages of the reversible MAOIs:

(a) an almost full biochemical effect is already present after the first dose;
(b) there is easy control over the effects of the drug;
(c) there is a distinct relationship between the plasma concentration of the drug and its pharmacological effect;
(d) only short-lasting carry-over effects occur.

There is a third possible mechanism by which the inhibition may occur with MAO — by competitive displacement of the substrate from MAO. This mechanism has been accepted (Carrier *et al*, 1982) as the mode of action of toloxatone (Fig. 6), but it has definite disadvantages for MAOIs with a short half-life, since there is only a very short duration of inhibitory activity, and thus only a short-lasting therapeutic action.

Specificity

The specificity of action of the new generation of MAOIs is much greater than that of the older compounds: they selectively inhibit either the A or the

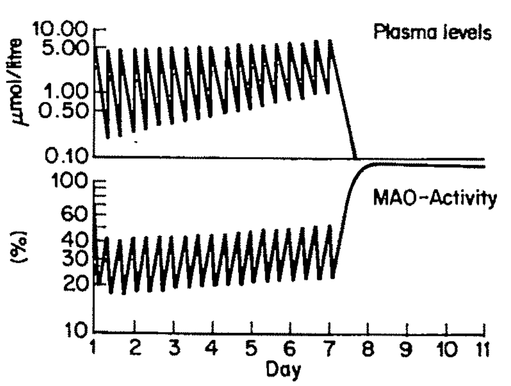

FIG. 5 Moclobemide (150 mg t.i.d.) plasma levels and MAO activity.

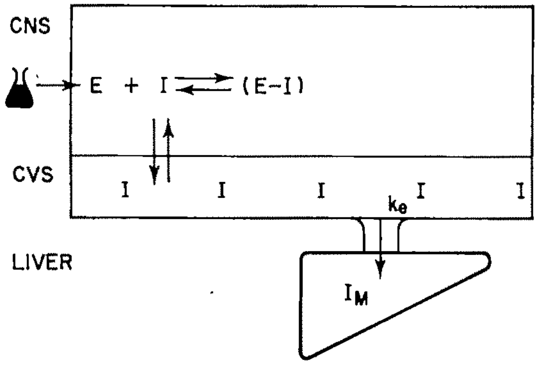

FIG. 6 Hypothetical model for binding characteristics (competitive displacement) of toloxatone and MAO. E: enzyme (MAO), I: inhibitor (toloxatone), k_e. rate constant for elimination, CNS: central nervous system, CVS: blood, I_M: inhibitor metabolite(s).

B form of MAO. However, in addition to the properties of selectivity and specificity, an ideal mechanism-based inhibitor should be inert, prior to binding exclusively to the specific reactive site on the enzyme, and this is certainly not the case with irreversible MAOIs of the hydrazine type. For example, though iproniazid was first used as a tuberculostatic drug (Bosworth, 1958; Davis, 1958), throughout its clinical development, many other clinical effects were observed, e.g. in rheumatoid arthritis and angina pectoris (Banghart, 1958); pain relief (Bateman, 1958; Lascelles, 1966), and in acne (Bateman, 1958); such effects cannot be explained by MAO inhibition. These favourable actions are no longer of clinical importance, since more specific and effective compounds have meanwhile been developed. However, some of the side-effects of the irreversible hydrazine MAOIs (Tollefson, 1983), such as orthostatic hypotension, hepatotoxicity, amphetamine-like actions, and anticholinergic effects, are important clinically. These types of unwanted effects have been observed primarily with iproniazid, but also partly with other hydrazine MAOIs; the fact that they are not caused by MAO inhibition, but by other mechanisms points to a lack of specificity of these earlier drugs.

Thus, there is no doubt that the hydrazine MAOIs produce additional, non-specific clinical effects which can also be understood in biochemical and pharmacological terms. They are characterised as highly reactive, and can have both alkylating and acetylating activity, as well as an inhibiting effect on diamino-oxidase, choline-oxidase, and different hydroxalases, methylases, and dealkylases. Of particular importance are their several and profound effects on the cytochrome P450 system (Tollefson, 1983). Animal experiments have shown that they also have direct stimulatory actions (Dourish *et al*, 1983).

The hepatotoxicity has in fact nothing to do with MAO inhibition, but is a result of the hydrazine structure of the molecule. Another hydrazine molecule, INH, which is widely used as a turberculostatic, has similar toxic effects, but no MAO inhibiting activity (Zimmermann & Ishak, 1987). Animal experiments (Schläppi, 1985; Burkard *et al*, 1989) have shown that under given conditions iproniazid has a hepatotoxic effect, whereas moclobemide showed no evidence of hepatotoxicity.

Chemically a benzamide derivative, moclobemide has an effect which seems to be specifically and almost exclusively that of MAO inhibition. Non-specific biochemical or pharmacological effects, such as have been described above for the hydrazine-type MAOIs, have not been found with moclobemide (Da Prada *et al*, 1989). The high specificity of moclobemide explains its much better tolerability, compared to the older MAOIs.

The occurrence of adverse events with moclobemide is hardly more frequent than with placebo. Figure 7 shows a comparison of adverse events from TCAs (Stabl *et al*, 1989) with those from moclobemide and from placebo.

In one large study (Rabkin *et al*, 1984), the tolerability of different MAOIs was compared; when these results are contrasted with those for moclobemide from placebo-controlled trials (Stabl *et al*, 1989), moclobemide has definitive advantages over phenelzine and tranylcypromine in terms of tolerability (Fig. 8), since moclobemide produces fewer side-effects than either of the comparative drugs.

The question whether the newer reversible MAOIs are in general highly specific drugs, which have no additional effects other than MAO inhibition, cannot yet be answered, since this group of drugs consists of

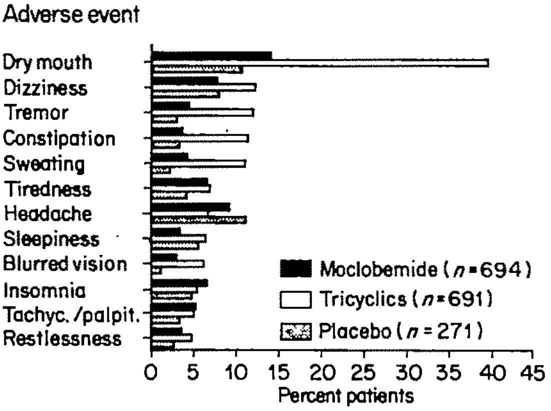

FIG. 7 Most common adverse events: data from double-blind studies where moclobemide was compared with tricyclic antidepressants and placebo (Stabl *et al*, 1989).

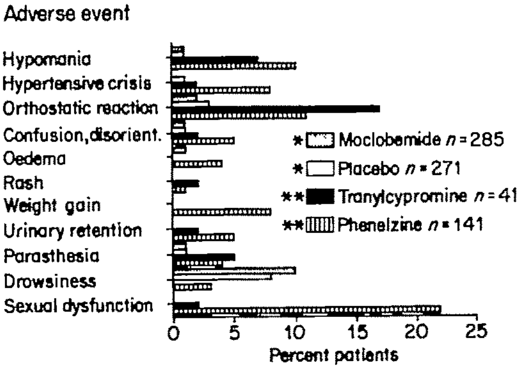

FIG. 8 Most common adverse events: historical comparison of moclobemide with tranylcypromine and phenelzine.
*Data from Stabl *et al* (1989). **Data from Rabkin *et al* (1984).

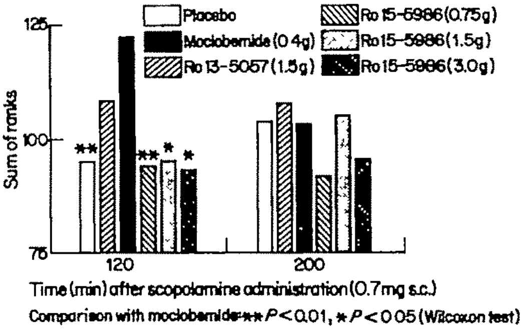

FIG. 9 Recovery from scopolamine-induced performance decrement. (Highest ranks indicate best recovery.)

substances from a large variety of chemical classes; the basic chemical structure is the decisive factor as to whether a given molecule influences biological processes other than those of MAO inhibition.

Additional attributes of moclobemide

Quite by chance, an additional attribute of moclobemide was discovered — one which could be of future clinical importance. The drug has been administered to elderly demented patients who were depressed (Postma & Vranesic, 1985; Kummer *et al*, 1989), and it was observed that during this treatment, there was improvement not only in the symptoms of depression but also in the cognitive impairment. This noticeable improvement in cognitive deficit in dementia was not thought clinically to be due only to the alleviation of depression.

Later, it was shown in the animal scopolamine model that the scopolamine-induced amnesia was alleviated (Martin *et al*, 1989), that mice learned more easily, and that the transcallosal evoked response was facilitated. In a human pharmacology model, single doses of different drugs were used to investigate the acute scopolamine-induced performance decrement (Anand & Wesnes, 1989). Several psychometric methods were used to assess the possible effects. In this model it was very surprising that a drug developed as an antidepressant should appear to be more effective than the piracetam analogues Ro 13-5057 and Ro 15-5986, which have been under investigation for a considerable time as possible improvers of cognitive performance (Fig. 9).

In a further study (Wesnes *et al*, 1989), it was shown that instead of potentiating alcohol-induced performance deficits, as do many other antidepressants, moclobemide actually reduced these deficits.

Discussion

The new, reversible MAOIs appear to have several advantages over the older, irreversible drugs. The onset of effect is rapid and this is then readily controlled through dose adjustment. There are no long-lasting carry-over effects on stopping treatment, which means that patients can switch from treatment with reversible MAOIs to another antidepressant treatment and vice versa without the need for a therapy-free interval. These advantages cannot be accounted for only by means of the pharmacokinetic properties, since all MAOIs are rapidly absorbed and are eliminated by hepatic metabolism. Furthermore, the elimination half-life of the old irreversible MAOIs is short (less than 3 h), whereas the elimination half-lives of the reversible MAOIs have much broader limits of variability (from less than 3 h to about 16 h depending on the MAOI). The elimination half-life of moclobemide is about 2 h. Single moclobemide doses 150 mg inhibit MAO for between 8 and 10 h. The full inhibitory effect is reached after administration of the first dose, and MAO activity is completely reinstated no later than 24 h after treatment.

The long duration of action of the old MAOIs occurs because of the irreversible covalent binding of inhibitor to enzyme. Binding characteristics for the new reversible MAOIs are thought to be different, however, and theoretical models have been proposed for tranylcypromine, moclobemide, and toloxatone to account for these differences.

Presumably as a consequence of the greater specificity of action of the new, reversible MAOIs, their clinical tolerability seems to be very satisfactory. In the case of moclobemide, studies comparing it with TCAs, with older MAOIs, and with placebo have shown that most types of side-effects are at a much lower level than with older active compounds. A favourable influence on scopolamine-induced performance decrements in healthy volunteers has been observed, as well as possible improvement in the manifestations of dementia in patients with both depression and dementia. However, the mechanisms underlying these effects are as yet unknown.

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A Double-blind Comparative Trial of Moclobemide v. Imipramine and Placebo in Major Depressive Episodes

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Patients ($n = 490$) suffering from a major depressive episode according to DSM-III criteria were randomly allocated to groups receiving either moclobemide, imipramine, or placebo treatment. Subjects were treated as out-patients for 6 weeks. On overall assessment of efficacy and on results of the Hamilton Rating Scale for Depression, both moclobemide and imipramine were superior to placebo, but the differences between moclobemide and imipramine were not significant. Premature termination due to insufficient efficacy was more frequent with placebo than with moclobemide or with imipramine, these differences being significant. The overall assessment of tolerance clearly favoured placebo and moclobemide over imipramine. This was also reflected in the frequency of premature terminations due to poor tolerance, as well as in the frequency of adverse events, which were highest in the imipramine group. The only cardiovascular finding was an increase of the mean heart rate with imipramine, maximum at the end of week 1, while placebo and moclobemide displayed no relevant changes. There were no other important drug-related changes.

Although monoamine oxidase inhibitors (MAOIs) were among the first substances to be used as antidepressants, they largely fell into disuse during the 1960s. The 'cheese effect' provoked by the interaction of these compounds with tyramine, a sympathomimetic substance which is a constituent of most diets, was among the principal reasons for this decline in the use of these drugs in the treatment of depression. As this interaction not uncommonly caused postural hypotension, the first MAOIs were increasingly superseded after the 1960s by tricyclic antidepressants (TCAs). These compounds, though, had their own adverse effects in the form of anticholinergic symptoms, cardiotoxicity, weight gain, and in some cases, sedation. A search for antidepressant drugs without serious adverse effects has therefore been in progress during the past 25 years.

Moclobemide is one of the new generation of MAOIs which is selective, in that it preferentially inhibits monoamine oxidase-A (MAO-A) and does not affect other enzyme systems. Furthermore, unlike classical MAOIs, it is characterised by reversibility of its inhibition of MAO (Keller *et al*, 1987). It therefore has the advantage of causing only minimal potentiation of the tyramine found in foodstuffs such as wine and cheese, so that 'cheese effects' are no more than mild and transient. Both animal and human pharmacological studies have established that no clinically significant interaction occurs if moclobemide is taken after consumption of tyramine in physiological amounts (Burkard *et al*, 1989; Gieschke *et al*, 1988; Schmid-Burgk *et al*, 1988).

Open-label clinical trials which involved about 600 patients suggested that moclobemide is well tolerated and possesses antidepressant efficacy in the dose range of 150–600 mg/day. Similar results were obtained in several double-blind studies v. placebo (Casacchia *et al*, 1984), clomipramine (Larsen *et al*, 1984), amitriptyline (Norman *et al*, 1985) and desipramine (Stefanis *et al*, 1984). In these comparisons, the antidepressant efficacy of moclobemide was found to be superior to that of placebo and not different from that of the TCAs. Moreover, the tolerability of moclobemide was superior to that of all the reference TCAs. However, due to the limited number of patients enrolled in each of these studies, it seemed necessary to confirm these results in a larger trial.

The aims of the present study were firstly to obtain further evidence concerning the antidepressant efficacy of moclobemide compared with placebo, and secondly to compare the efficacy and tolerability of moclobemide with those of imipramine. In order to obtain a sample of patients adequate in size to yield a body of evidence that could be expected to answer the questions asked, the study was conducted on a multicentre basis.

Method

A total of 490 patients was enrolled in this double-blind, prospective, randomised, 6-week multicentre study; those considered for participation were men or non-pregnant and non-lactating women, aged 18 to 65 years. Patients were required to meet the DSM-III criteria for a major depressive episode and to have a minimum baseline score of 17 on the 21-item Hamilton Rating Scale for Depression (HRSD). Once enrolled in the study, their depression was further categorised according to the ICD-9 classification; however, depressive subtype did not affect either inclusion in or exclusion from the study. Patients receiving lithium could be enrolled in the study, providing treatment had been stabilised for at least 4 weeks prior to entry. Exclusion criteria were: marked suicidal intent (since out-patients could be enrolled in the study), other psychiatric illness, severe organic disease, alcoholism, and drug abuse. In addition, patients were required not to have the usual contraindications to treatment with TCAs. All patients gave informed consent to the study.

On inclusion (there was no run-in period), patients were randomly allocated within each study centre to either moclobemide ($n = 164$), imipramine ($n = 164$), or placebo ($n = 162$). Patients received capsules of identical appearance and taste, containing either 100 mg of moclobemide, or 33.3 mg of imipramine, or placebo. Trial medication was blister-packaged; the initial daily dosage was three capsules per day, and could be increased to six daily, after 5 days of treatment, providing tolerability was satisfactory. Thus for moclobemide, the initial daily dosage was 300 mg, which could be increased to 600 mg. For imipramine, the daily dosage was increased progressively during the first 4 study days, and to guarantee double-blind conditions, imipramine capsules were supplemented with placebo. Thus, the daily dosage was increased from 33.3 mg (placebo-placebo-33.3 mg) on day 1, to 66.6 mg (33.3 mg-placebo-33.3 mg) on day 2, and to 100 mg (33.3 mg-33.3 mg-33.3 mg) on day 4; it could be further increased to 200 mg/day (i.e. six capsules/day).

The use of concomitant psychotropic medication was prohibited, with the exception of lithium for those patients on previously established therapy with it, and of a benzodiazepine if judged necessary by the investigator. During the study, patients were not required to avoid tyramine-rich foods.

The efficacy and safety of treatment were evaluated on study days 3, 7, 14, 21, 28 and 42. Efficacy was judged primarily on the 17-item HRSD, and on an investigator's final overall assessment of efficacy. Tolerability was judged on the number and severity of both reported and observed adverse events, on the investigator's final overall assessment of tolerability, and on vital signs (blood pressure and heart rate, supine and standing; body weight). A physical examination was performed on entry to the study and at the end of treatment. An ECG and a laboratory screen, including haematology (haemoglobin, erythrocytes, leucocytes and differential, platelets), clinical chemistry (bilirubin, creatinine, urea, blood glucose, alkaline phosphatase, SGOT, SGPT, gamma-GT), and urine analysis (glucose, protein), were performed on entry to the study, after 2 and 4 weeks, and at the end of treatment.

Results

On inclusion, all three treatment groups were comparable for demographic and illness characteristics, as well as for mean baseline HRSD scores (Table I; Fig. 1). Approximately half the patients were diagnosed as suffering from endogenous depression (Table I).

The number of subjects who were withdrawn prematurely from the study was comparable for moclobemide and for imipramine respectively, but was higher with placebo (Table II). The number withdrawn because of insufficient efficacy (Table II) was higher with placebo than with moclobemide ($P = 0.001$; Fisher's exact test) or than with imipramine

TABLE I

Baseline demographic and illness characteristics of 490 depressed patients randomly allocated to either moclobemide (n=164), imipramine (n=164) or placebo (n=162)

	Treatment group		
Characteristic	*Moclobemide*	*Imipramine*	*Placebo*
Age (mean ± s.d.) (years)	44 ± 12	42 ± 12	42 ± 12
range	19–67	20–69	18–66
Sex			
no. of males	40	38	39
no. of females	124	126	123
Weight (mean ± s.d.) (kg)	62 ± 11	62 ± 12	63 ± 12
No. of patients with[1]:			
endogenous depression (monopolar)	69	75	68
endogenous depression (bipolar)	13	6	9
neurotic/reactive depression	75	77	77
other[2]	7	6	8
Mean (± s.d.) total score on the first 17 items of the HRSD	26 ± 5.4	25.5 ± 5.1	25.4 ± 5.0

1. Patients were enrolled in the study on a diagnosis of a major depressive episode (DSM-III). Once they were enrolled in the study, the investigator categorised their depression according to the ICD-9 classification, but depressive subtype did not influence either inclusion in or exclusion from the study.
2. Moclobemide: organic/symptomatic depression (2), depression in schizophrenia (2), neurasthenia (1), major depression unspecified (2).

Imipramine: organic/symptomatic depression (3), depression in schizophrenia (1), major depression unspecified (2).

Placebo: organic/symptomatic depression (2), depression in schizophrenia (2), neurasthenia (2), depression unspecified (2).

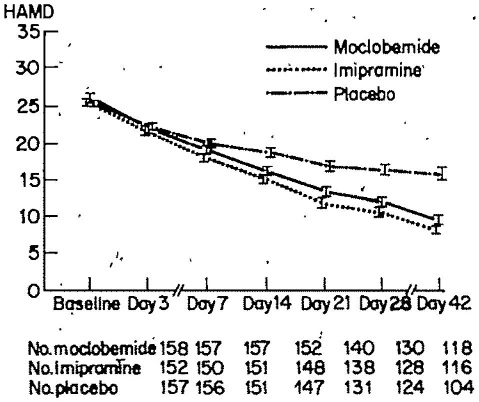

FIG 1 Mean values of total scores of HRSD (17 items) for the three groups over the entire treatment period. Drop-outs are included until they left the study.

($P = 0.002$; Fisher's exact test). Poor tolerability was given as the reason for withdrawal in 7% of patients on imipramine ($P = 0.005$ v. placebo), but in only 3% of patients on moclobemide ($P = 0.37$ v. placebo), and 1% of patients on placebo.

The dose of study medication was increased in most patients after the first week of treatment: by the end of the second week, the mean daily dosage was 509 mg with moclobemide and 159 mg with imipramine, then remaining constant until the end of the study. A total of 90 patients taking moclobemide, compared with 80 taking imipramine and 82 taking placebo, were treated concomitantly with a benzodiazepine. One patient in the moclobemide group and two in the imipramine group were receiving lithium on entry, and continued to be treated with it throughout the study.

As shown in Fig. 1, both moclobemide and imipramine were more effective in reducing depressive symptoms than was placebo, as judged by the total score on the HRSD. The mean final percentage reduction of total HRSD score was 52% with moclobemide, 56% with imipramine, and 28% with placebo. The differences between imipramine and placebo, as well as between moclobemide and placebo, were significant ($P < 0.001$; Kruskal-Wallis test). However, there was no significant difference between moclobemide and imipramine ($P = 0.26$; Wilcoxon two-sample test). Analysis of only those patients who completed the trial yielded a mean final improvement of 61.8% for the moclobemide group, 66.4% for the imipramine group and 37.3% for the placebo group. The differences were significant according to the Kruskal-Wallis test ($P = 0.0001$) — equally significant between moclobemide and placebo (Wilcoxon two-sample test, $P = 0.0001$) and between imipramine and placebo. There was no significant difference, though, between moclobemide and imipramine ($P = 0.14$).

The investigators' final assessments of efficacy showed that this was judged to be good or very good in 70% of patients taking moclobemide, 70% of patients taking imipramine, and 28% of those taking placebo (Table III). Moclobemide appeared to be as effective as imipramine in endogenous depression, and a little less effective than imipramine in neurotic/reactive depression (Table IV). The response rate, defined as the percentage of patients whose total score on the first 17 items of the HRSD was reduced by 50% or more at the end of treatment, was not affected by concomitant benzodiazepine treatment (Table IV).

The investigators' global overall assessments of tolerability favoured placebo over moclobemide ($P = 0.005$; Stucky-Vollmar test) and moclobemide over imipramine ($P = 0.0004$). Thus, tolerability was judged to be good or very good in 85% of patients taking moclobemide, 74% of patients taking imipramine, and 91% of those taking placebo. Adverse events were reported in 67% of patients taking moclobemide, compared with 78% of patients taking imipramine and 54% of those taking placebo. Only insomnia, dry mouth, epigastric discomfort, and nausea were seen more frequently with moclobemide than with placebo, and only insomnia was reported more frequently for moclobemide than for imipramine (Fig. 2). The overall incidence of anticholinergic adverse events was higher with imipramine than with moclobemide. The total number of severe adverse events was higher with imipramine than with moclobemide (78 v. 40), and was lower with placebo (28).

There was a slight increase of heart rate (on average 3 beats/min) and a decrease of systolic blood pressure (on average 6 mmHg) with imipramine, while with moclobemide and with placebo, the corresponding values remained practically unchanged. The mean values of diastolic blood pressure remained unchanged in all three groups: there was no difference between the groups in the number of individual patients in whom hyper- or hypotensive blood pressure values were recorded.

TABLE II

Premature termination of treatment with reasons as stated by the investigator

	Moclobemide (*n=164*) (%)	*Imipramine* (*n=164*) (%)	*Placebo* (*n=162*) (%)
Insufficient efficacy	11	12	25
Poor tolerability	3	7	1
Intercurrent disease	2	1	1
Other non-drug-related reasons	10	9	9
Total	26	29	36

TABLE III
Investigators' overall assessments of efficacy and tolerance at the end of treatement

	Moclobemide *No. (%)*	*Imipramine* *No. (%)*	*Placebo* *No. (%)*
Efficacy			
Final assessment			
very good	57 (36.1)	60 (39.5)	19 (12.2)
good	53 (33.5)	47 (30.9)	24 (15.4)
moderate	19 (12.0)	17 (11.2)	44 (28.2)
no change or worse	29 (18.4)	28 (18.4)	69 (44.2)
No. classified[1]	158 (100)	152 (100)	156 (100)
Not assessed	0	0	1
Tolerance			
Final assessment			
very good	73 (44.5)	40 (24.5)	100 (62.1)
good	66 (40.2)	80 (49.1)	47 (29.2)
moderate	20 (12.2)	31 (19.0)	12 (7.5)
poor	5 (3.0)	12 (7.4)	2 (1.2)
No. classified	164 (100)	163 (100)	161 (100)
Not assessed	0	1	1

1. Six patients in the moclobemide group, 12 patients in the imipramine group, and five patients in the placebo group were excluded from the standard efficacy analysis because of protocol violations and/or less than 7 days of treatment.

TABLE IV
Number of patients and percentage responders (defined as a ≥50% final improvement on the 17-item HRSD) and mean final improvement (±s.d.) on this scale presented for all patients as well as for the subsamples endogenous/reactive-neurotic depressives and concomitant benzodiazepine treatment

	Responders		
	Moclobemide	*Imipramine*	*Placebo*
Patient group	*No. % resp.*	*No. % resp.*	*No. % resp.*
All patients[1]	158 (63%)	152 (68%)	157 (29%)
Endogenous (mono- and bipolar)	81 (64%)	76 (55%)	75 (28%)
Neurotic/reactive	74 (58%)	73 (66%)	77 (32%)
Patients on benzodiazepines	79 (61%)	72 (53%)	76 (33%)
Patients not on benzodiazepines	79 (61%)	80 (66%)	81 (28%)
	Final improvement (mean ± s.d.) %		
All patients[1]	51.9 ± 33.8	56.1 ± 32.4	28.5 ± 33.5
Endogenous (mono- and bipolar)	50.9 ± 31.7	51.7 ± 31.4	29.0 ± 29.7
Neurotic/reactive	45.1 ± 32.0	53.0 ± 29.9	29.3 ± 36.1
Patients on benzodiazepines	47.3 ± 32.4	44.0 ± 31.8	34.3 ± 34.0
Patients not on benzodiazepines	48.6 ± 31.7	58.7 ± 28.4	25.2 ± 30.7

1. Six patients in the moclobemide group, 12 patients in the imipramine group, and five patients in the placebo group were excluded from the standard efficacy analysis because of protocol violations and/or less than 7 days of treatment.

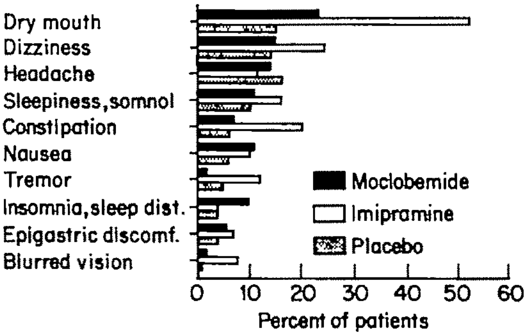

FIG 2 Frequency of occurrence (%) of the most frequent side-effects in the three treatment groups.

In a few individual cases in each treatment group, some isolated laboratory findings beyond the normal range were recorded. The great majority of these were considered medically non-relevant, and in none did they prove on the basis of subsequent observations to be treatment-related.

Discussion

The more serious nature of the side-effects of imipramine, compared with moclobemide, which emerged in this study, has particular importance at the present time regarding the data published by Kilch *et al* (1988) and by Lee & Murray (1988). In these follow-up studies, over a period of 15–20 years, both endogenous and 'neurotic' forms of depression proved to be disorders subject to either repeated relapse with frequent hospital admissions in a high proportion of cases, or else likely to pursue a chronic and unremitting course.

Therefore, it has to be assumed that the treatment of patients with drugs that have proved to be effective (in combination with other measures) might have to extend, albeit intermittently, for periods of years or decades. Considerably greater weight than in the past must therefore be attached at the present time to any serious side-effects of drugs which may be employed in the management of depressive illness.

A number of steps were taken to ensure that the patients admitted to the present study would constitute prognostically a relatively homogenous group, in order to minimise the risk of positive therapeutic results being obscured through dilution of the patient population by cases with conditions unrelated to the depressive disorders under enquiry. To this end, prior to the initiation of the trial and throughout its course, meetings of the participating investigators were held, with a view to achieving consistency in the application of diagnostic criteria, in utilisation of the HRSD, and in the standardisation of practices relating to doses and interpretation of side-effects. As the countries in which the trial was undertaken also had some common sociocultural characteristics, there was felt to be sufficient uniformity in the patients enrolled to justify summation of the findings recorded at the different centres. Data obtained in the entire population were therefore submitted for a single statistical analysis.

Results of the global judgement of antidepressant efficacy approximate closely to the usual success rate of 60–70% that has been registered in trials of TCAs of proven efficacy. A slightly lower success rate, reflected in the results on the HRSD, was found in the moclobemide group and also in relation to imipramine — a standard TCA whose efficacy has been established over a period of 30 years. Account has to be taken here of the fact that the sample of patients enrolled included non-endogenous as well as endogenous cases of depression, as judged by ICD-9 criteria.

Although benzodiazepines had been prescribed slightly more frequently in the moclobemide group, they exerted no confounding effect on the efficacy findings; there was no difference in outcome between those patients in the moclobemide group who had and those who had not been given a benzodiazepine.

Analysis of the subsample of patients with endogenous depression according to ICD-9 showed that the efficacy of moclobemide was equal to that of imipramine in respect of the rate of improvement at the end of the trial. In neurotic depression, however, imipramine proved slightly more effective, although the results with moclobemide were significantly superior to those of placebo. Moclobemide therefore appears to be an effective compound in the treatment of depressive disorders overall.

This result is of interest in relation to the outcome of the large therapeutic trial of antidepressants undertaken by the British Medical Research Council (1965); endogenous cases must have predominated in that sample, due to the admission criteria employed. In that study, the MAOI phenelzine was stated to be devoid of efficacy for the treatment of depressive disorders, whereas in contrast, the therapeutic efficacy of imipramine was confirmed. This verdict probably played a considerable part in the steep decline in the use of conventional MAOIs from the 1960s onwards, although it has been rebutted as far as the MAO-A inhibitor is concerned.

In the present study, although moclobemide and imipramine achieved successful results in a similar proportion of cases, this does not necessarily signify that the patients who responded well in the two groups had identical clinical profiles. A detailed comparison of responders in the two groups has yet to be undertaken, but pending the more precise indications that may emerge from such studies, moclobemide already seems to deserve a place, among drugs of choice in the treatment of depressive illness, on the strength of existing results. It should also be worthy of trial in those cases which have proved refractory to conventional forms of antidepressant treatment.

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Efficacy and Tolerability of Moclobemide Compared with Imipramine in Depressive Disorder (DSM-III): An Austrian Double-blind, Multicentre Study*

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The antidepressant efficacy, tolerability, and safety of moclobemide, a reversible, monoamine oxidase-A inhibitor, were compared with those of imipramine in parallel groups of patients with a major depressive episode, in a 4-week, multicentre (17 centres), randomised study. A total of 381 patients were randomly allocated to either treatment; they were not required to avoid tyramine-rich foods. Drop-out rates were comparable in both groups at about 17%. Judged primarily on the HRSD, no significant differences in efficacy were observed between the groups, but the number of patients presenting with adverse events, as well as the total number of adverse events, was greater with imipramine. Cardiovascular tolerability was satisfactory and physical examination, body weight, and laboratory values were essentially unaffected in both groups.

Irreversible monoamine oxidase inhibitors (MAOIs) were the first drugs to be recognised as effective in the treatment of depression (Crane, 1957). However, MAOIs fell into fairly general disuse soon after their introduction, mainly because they were considered to be less effective than tricyclic antidepressants (TCAs) (West & Dally, 1959). This seemed to be particularly true for endogenous depression: phenelzine was reported to be effective in 70% of patients with depressive neurosis, but in only 18% of patients with endogenous depression (Paykel, 1971). MAOIs also became somewhat discredited because of the occurrence of hypertensive crises after exposure to foods containing tyramine (Horwitz *et al*, 1964). In recent years, reversible MAOIs have been discovered, and have attracted great interest, as the risk with them of hypertensive crisis appears to be less.

Moclobemide is a novel compound which belongs to this new class of reversible monoamine oxidase-A (MAO-A) (Da Prada *et al*, 1989). It has been shown to be a weak potentiator of the pressor effects of orally administered tyramine (Gieschke *et al*, 1988; Korn *et al*, 1988; Müller *et al*, 1988; Burgess & Mellsop, 1989) and to be more effective than placebo for the treatment of a major depressive episode (Versiani *et al*, 1989).

The question remained, however, as to whether this type of compound could be as effective as TCAs for the treatment of depression. Here, we report the results obtained in a prospective, double-blind study, comparing the antidepressant efficacy of moclobemide with that of imipramine in parallel groups of patients suffering from a major depressive episode, as defined by DSM-III.

Method

A total of 381 patients was enrolled in this double-blind, prospective, randomised, multicentre study, over a 24-month period. Patients considered for participation were men or non-pregnant and non-lactating women, over 18 years of age. Patients were required to meet the DSM-III criteria for a major depressive episode and to have a minimum baseline score of 17 on the 21-item Hamilton Rating Scale for Depression (HRSD). Once the patients were enrolled in the study, their depression was further categorised according to the ICD-9 classification, but depressive subtype did not affect either inclusion in or exclusion from the study. Patients on lithium could be enrolled in the study, providing lithium plasma levels were within the normal therapeutic range, and treatment had been stabilised for at least 4 weeks prior to entry into the study. Patients who had received antidepressant treatment (with the exception of imipramine) could be enrolled in the study after a 3–5 day washout period, providing treatment had not been effective, and/or was not well tolerated. Exclusion criteria were as follows: marked suicidal intent (because out-patients could be enrolled in the study), other psychiatric illness, alcoholism, drug abuse, and women in whom pregnancy could not be excluded during the trial. In addition, patients were required not to have the usual contra-indications to treatment with TCAs. All patients gave their consent to the study.

On inclusion (there was no run-in period), patients were randomly allocated within each study centre to either moclobemide ($n=189$) or to imipramine ($n=192$). Moclobemide, 100 mg capsules, and imipramine, 33.3 mg capsules of identical appearance were used.

The trial drugs were given three times daily (morning, noon, and evening). Treatment was started with 300 mg/day of moclobemide (100 mg–100 mg–100 mg) or 33.3 mg/day of imipramine (placebo–placebo–33.3 mg). Moclobemide dosage was kept constant, while imipramine dosage was increased to

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*Participants included H. Donat (Wien), B. Gallhofer (Graz), P. König (Rankweil), H. Pfolz (Wien), H. Pietschmann (Wien), T. Platz (Klagenfurt), L. Rieder (Wien), M. Saletu (Wien), G. Schnaberth/J. Bruck (Wien), W. Schöny (Linz), H. Schubert (Hall in Tirol), R. Wolf (Wien).

66 mg/day on day 2 (33.3 mg–placebo–33.3 mg) and to 100 mg/day on day 4 (33.3 mg–33.3 mg–33.3 mg). Between days 6 and 14, the daily target dose of moclobemide was 400 mg (200 mg–100 mg–100 mg) and of imipramine 133 mg (66.6 mg–33.3 mg–33.3 mg). Between days 15 and 28, dosage could be further increased up to a maximum of 600 mg/day of moclobemide (200 mg–200 mg–200 mg) or 200 mg/day of imipramine (66.6 mg–66.6 mg–66.6 mg), providing tolerability was satisfactory and efficacy at the prevailing level seemed to be insufficient.

The use of concomitant psychotropic medication was prohibited, with the exception of lithium, for patients on previously established lithium regime, or benzodiazepine, if judged clinically necessary by the investigator. During the study, patients were not required to avoid tyramine-rich foods.

The efficacy and safety of treatment were evaluated on study days 3, 7, 14, 21, and 28. Efficacy was judged primarily on the 17-item HRSD, and on an investigator's final overall assessment of efficacy. Tolerability was judged on the number and severity of reported and observed adverse events, on investigator's final overall assessment of tolerability, and on vital signs (blood pressure and heart rate, supine and standing; body weight). A physical examination was performed on entry to the study and at the end of treatment. An ECG and laboratory screen, including haematology (haemoglobin, erythrocytes, leucocytes, neutrophils, eosinophils, basophils, monocytes, lymphocytes, platelets), clinical chemistry (bilirubin, creatinine, urea, blood glucose, alkaline phosphatase, SGOT, SGPT, γ-GT), and urine analyses (glucose, protein, haemoglobin/erythrocytes), were performed on entry, after 2 weeks, and at the end of treatment.

Results

On entry to the study, both treatment groups were comparable for demographic and illness characteristics, as well as for baseline HRSD scores (Table I; Fig. 1). A little over half the patients were judged to suffer from endogenous-type depression (Table I). Of the 17 centres which participated in the study, two enrolled only elderly patients, explaining the relatively high proportion of patients over 60 years of age in the sample (Table I).

Drop-out rates and reasons for premature termination of treatment were comparable in both treatment groups (Table II), although there was a non-significant trend ($P = 0.082$, Fisher's Exact Test) towards more patients being withdrawn for insufficient efficacy in the moclobemide than in the imipramine group.

Approximately 65% of patients in each treatment group (119 patients in the moclobemide group and 128 patients in the imipramine group) were treated concomitantly with a benzodiazepine. In addition, seven patients in the moclobemide group and three in the imipramine group were taking lithium therapy on entry to the study, and continued to receive lithium throughout the trial.

The data from eight patients in the moclobemide group and from 13 patients in the imipramine group were excluded from the standard efficacy analysis, either because of protocol violations (having an initial HRSD score more than two points below the criterion specified in the protocol, non-fulfillment of DSM-III criteria for a major depressive episode, presence of mood-incongruent delusions or hallucinations on entry, neuroleptic co-medication) or because the patients were treated for less than 7 days.

The standard efficacy analysis included all the other patients, irrespective of their duration of treatment. Both moclobemide and imipramine were associated with a significant reduction in the depressive symptomatology as judged by total HRSD (17 items) scores (Fig. 1). No significant differences were observed between the treatment groups; it was notable that the onset of action seemed to be comparable in both groups. The mean percentage reduction of the HRSD at the end of treatment

TABLE I

Baseline demographic and illness characteristics of 381 depressed patients randomly allocated to either moclobemide (n=189) or imipramine (n=192)

	Treatment group	
Characteristic	*Moclobemide*	*Imipramine*
Age (mean ± s.d.) years:	53.4 ± 17.8	55.6 ± 16.7
range	23–97	20–96
No. of patients		
under 60 years	128	116
over 60 years	61	76
Sex:		
no. of males/age range	48/23–88	49/20–74
no. of females/age range	141/24–97	143/21–96
Weight (mean ± s.d.) (kg)	68.3 ± 13.3	68.4 ± 13.1
No. of:		
in-patients	122	120
out-patients	37	36
in- and out-patients	30	36
No. of patients with[1]:		
endogenous monopolar depression	93	97
endogenous bipolar depression	18	15
neurotic/reactive depression	46	41
organic/symptomatic depression[2]	27	32
other[3]	5	7
Mean (± SD) total score on the first 17 items of the HRSD	25.0 ± 5.7	24.3 ± 5.9

1. Patients were enrolled in the study on a diagnosis of a major depressive episode (DSM-III). Once they were enrolled in the study the investigator categorised their depression according to the ICD-9 classification, but depressive subtype did not influence either inclusion in or exclusion from the study.

2. This was seen predominantly in geriatric patients, and was associated with cerebral atherosclerosis or a history of stroke.

3. Moclobemide: post-psychotic depression in schizophrenia (2), neurasthenia (1), endo-reactive depression (1), chronic depression unspecified (1).

Imipramine: post-psychotic depression in schizophrenia (4), neurasthenia (3).

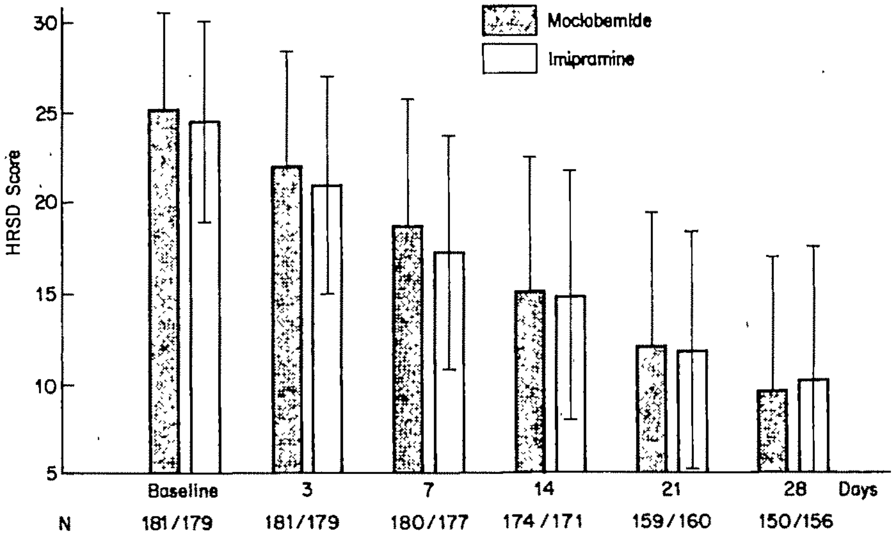


FIG. 1 Mean (±s.d.) total scores on the first 17 items of the HRSD throughout the study for 360 depressed patients during treatment with either moclobemide or imipramine.

TABLE II
Reasons for premature termination of treatment in 381 depressed patients treated either with moclobemide (n=189) or with imipramine (n=192)

	Treatment group	
Reason	*Moclobemide* No. (%)	*Imipramine* No. (%)
Recovery	2 (1.1)	2 (1.0)
Manic switch	1 (0.5)	—
Suicidal attempt	1 (0.5)	2 (1.0)
Suicidal ideation	1 (0.5)	1 (0.5)
Insufficient efficacy	15 (7.9)	7 (3.6)
Poor tolerability	9 (4.8)	7 (3.6)
Intercurrent disease	1 (1.1)	—
Other[1]	5 (2.6)	11 (5.7)
Total	35 (19)	31 (16)

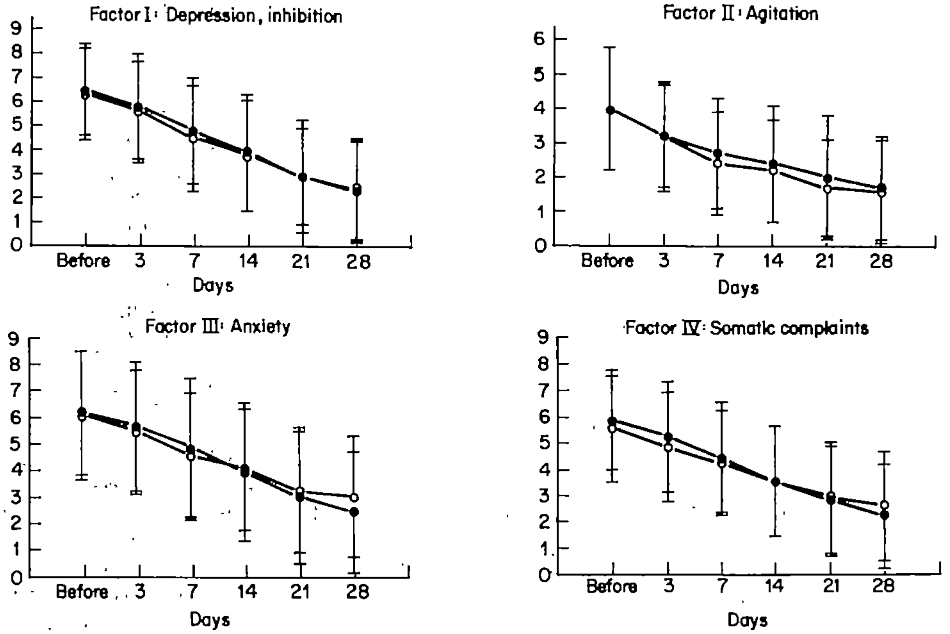
[1] Failure to return, or drug refusal.

was 51.7% in the moclobemide group and 52.1% in the imipramine group. Factorial evaluation of the HRSD (Fig. 2) failed to show any substantial difference between the efficacy of moclobemide and that of imipramine on any of the four factors.

The response rate, defined as the percentage of patients whose total score on the first 17 items of the HRSD was reduced by 50% at the end of treatment, appeared to be comparable in the two groups; subgroup analyses recording type of depression, sex, and age, did not reveal any relevant differences between the treatment groups (Table III). Interestingly, the response rate was lower, in both treatment groups, in the patients who had received benzodiazepines than in those who had not received benzodiazepines. The investigator's final overall assessment of efficacy (Table IV) yielded results which were in good agreement with those obtained by analysing the response rate on the HRSD.

Treatment tolerability and safety were judged on reported and observed adverse events, an investigator's final overall assessment of tolerability, vital signs, physical examination, ECG, and a laboratory screen. Adverse events were reported and observed in significantly more patients taking imipramine (69%) than moclobemide (56%; $P = 0.008$, Fisher's Exact Test). The investigator's overall judgement on tolerability also significantly favoured moclobemide over imipramine ($P = 0.005$, Stucky-Vollmar Test; Table V). The total number of adverse events, irrespective of severity, was higher with imipramine than with moclobemide (total: 286 v. 189; mild and moderate: 215 v. 150; severe: 71 v. 39). The difference in tolerability between imipramine and moclobemide appeared to be due mainly to the higher incidence of anticholinergic adverse events with imipramine (Fig. 3).

Therapy with first-generation MAOIs has been reported to induce a typical pattern of central nervous system side-effects characterised by insomnia, irritability, agitation, motor restlessness, and hypomania (see e.g. Kline & Cooper, 1980). In this study, the adverse events induced by moclobemide were mainly sleep disturbances and restlessness; the incidence of these, however, seemed to be comparable in both treatment groups (Table VI). Autonomic side-effects observed with first-generation MAOIs included dry mouth, constipation, dizziness, orthostatic hypotension, and delayed ejaculation, but in this study, the incidence of these effects was greater with imipramine than with moclobemide (Table VI). Cardiovascular tolerability was satisfactory in both groups, tachycardia and hypotension being reported a little more frequently with imipramine than with moclobemide (Fig. 3). ECG anomalies (a conductance defect) developed in one patient taking imipramine. One 53-year-old, female in-patient taking moclobemide was reported to have an asymptomatic 40 mmHg increase in systolic blood pressure values 2 h after her morning dose of moclobemide on study day 7. Her blood pressure values



Factor I: Depression, inhibition

Factor II: Agitation

Factor III: Anxiety

Factor IV: Somatic complaints

FIG. 2 Mean (±s.d.) values on the four factors of the HRSD throughout the study for 360 depressed patients during treatment with either moclobemide (●—●) or imipramine (o—o).

TABLE III

Percentage of patients with a ≥50% decrease of their total score on the first 17 items of the HRSD at end of treatment as a function of diagnostic and demographic characteristics, or of concomitant treatment

	Treatment group			
	Moclobemide		*Imipramine*	
Patient group	*No.*	*Responders (%)*	*No.*	*Responders (%)*
All patients[1]	180	58	179	58
Patients with:				
endogenous monopolar depression	90	64	92	71
endogenous bipolar depression	17	53	15	60
neurotic/reactive depression	44	55	40	55
organic/symptomatic depression	25	52	28	25
Patients:				
over 60 years	54	52	67	52
under 60 years	126	61	112	62
Males	45	67	46	76
Females	135	55	133	52
Patients taking benzodiazepines[2]	112	50	121	55
Patients not taking benzodiazepines	68	69	58	66
Patients taking lithium	7	28	3	100

1. Eight patients in the moclobemide group and 13 patients in the imipramine group were excluded from the standard efficacy analysis (for further details, see Results); one patient in the moclobemide group was treated for 7 days, but not assessed.
2. In most patients the benzodiazepines were either nitrazepam or diazepam given throughout the study.

TABLE IV
Investigator's final overall assessment of efficacy in 359 depressed patients treated with either moclobemide or imipramine

Investigator's assessment	*Treatment group* *Moclobemide* (n=*181*)[1] *No. (%)*	 *Imipramine* (n=*178*)[1] *No. (%)*
Very good	53 (29)	41 (23)
Good	60 (33)	66 (37)
Moderate	41 (23)	53 (30)
No change or worse	27 (15)	18 (10)

1. Number of patients/group; eight patients in the moclobemide group and 13 patients in the imipramine group were excluded from the standard efficacy analysis (for further details, see Results); one patient in the imipramine group was not assessed.

TABLE V
Investigator's final overall assessment of tolerability in 379 depressed patients treated with either moclobemide or imipramine

Investigator's assessment	*Treatment group* *Moclobemide* (n=*189*)[1] *No. (%)*	 *Imipramine* (n=*190*)[1] *No. (%)*
Very good	96 (51)	63 (33)
Good	61 (32)	79 (42)
Moderate	18 (10)	31 (16)
Poor	14 (7)	17 (9)

1. Number of patients/group; two patients in the imipramine group were not assessed.

returned to normal within a few hours without any particular treatment, and the patient continued to be treated with moclobemide without any other increases in blood pressure.

Physical examination, body weight and laboratory values were not affected in a clinically relevant fashion in either treatment group.

Discussion

This study shows that the antidepressant efficacy of moclobemide is comparable to imipramine in patients suffering from a major depressive episode. However, the tolerability of moclobemide was superior to that of imipramine.

On entry to the study, both treatment groups were comparable for demographic and illness characteristics, affording valid comparisons between the groups. One of the major criticisms, however, which could be made of this study, is that a high proportion of patients (approximately 65%) were treated concomitantly with a benzodiazepine. This reflects the habit, in certain European countries, of prescribing a benzodiazepine together with an antidepressant drug, but does not simplify the interpretation of results. Efficacy was judged primarily on the HRSD and on the investigator's final global assessment of efficacy. No significant differences between the two treatment groups were observed, yet the number of patients enrolled in each group (i.e. 189 in the moclobemide group and 192 in

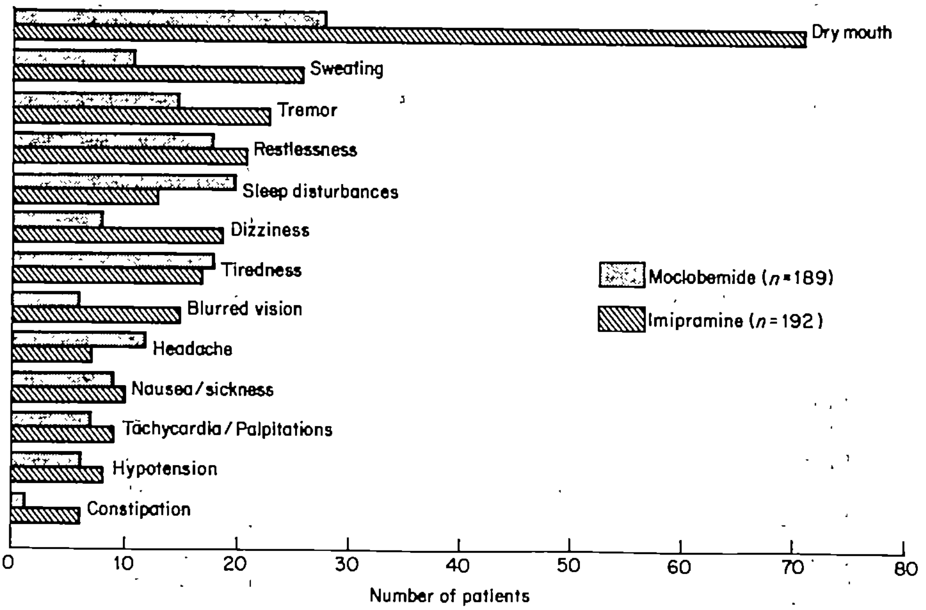


FIG. 3 Most commonly reported and/or observed adverse events in 381 depressed patients treated with either moclobemide or imipramine.

TABLE VI

Incidence of classical CNS and autonomic MAOI-type adverse events in 381 depressed patients treated with either moclobemide (n=189) or imipramine (n=192)

	Treatment group	
Reported and/or observed adverse effects	*Moclobemide No. (%)*	*Imipramine No. (%)*
CNS		
sleep disturbances	20 (10.6)	13 (6.8)
irritability/excitation	1 (0.5)	1 (0.5)
agitation (increased)	1 (0.5)	2 (0.5)
restlessness/nervousness	18 (9.5)	21 (10.9)
hypomania	2 (1.0)	1 (0.5)
Autonomic		
dry mouth	28 (14.8)	71 (37.0)
constipation	1 (0.5)	6 (3.0)
dizziness	8 (4.2)	19 (9.9)
hypotension (orthostatic)	6 (3.2)	8 (4.2)
delayed ejaculation	—	1 (0.5)

the imipramine group) would have been sufficient to detect a $>12\%$ difference in response rate ($2\alpha = 0.05$, power $= 80\%$, $N1 = N2 = 190$, response rate $= 60\%$). Thus, it can be concluded that the antidepressant efficacy of moclobemide is unlikely to be very different from that of imipramine.

First-generation MAOIs have been reported not to be effective in endogenous depression (West & Dally, 1959; Paykel, 1971; Davidson *et al*, 1978; Robinson *et al*, 1978) but in the present study, moclobemide was not shown to differ from imipramine in efficacy in such cases. This result should, however, be interpreted with caution, because analysis of the subgroups was retrospective and the diagnosis of depressive subtypes was based only on the ICD-9 classification.

The tolerability of moclobemide was found to be significantly superior to that of imipramine; this seemed to be mainly due to the higher incidence of anticholinergic adverse events with imipramine. Moclobemide did not induce the typical spectrum of central and autonomic nervous system side-effects which is characteristic of first-generation MAOIs. The cardiovascular tolerability of both drugs was comparable, and no typical acute elevations of blood pressure were reported, even though no dietary restrictions had been given to the patients.

In conclusion, moclobemide, an MAOI which differs from first-generation MAOIs by the fact that it is reversible and selective for MAO-A, was not shown to differ in efficacy from imipramine in the treatment of depression, including endogenous depression, but was significantly better tolerated. Moreover, moclobemide does not induce the typical side-effect profile observed with first-generation MAOIs.

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Pre-clinical Pharmacology of Moclobemide

A Review of Published Studies

WILLY P. BURKARD, MOSÉ DA PRADA, HANS H. KELLER, ROLF KETTLER and WILLY HAEFELY

The novel antidepressant, moclobemide, is a reversible inhibitor of monoamine oxidase (MAO) preferentially of monoamine oxidise-A (MAO-A); it emerged for study out of a series of lipid-lowering agents. In spite of its weak MAO-A inhibition *in vitro*, moclobemide is a potent inhibitor of MAO-A, *in vivo*; its *in vivo* activity is of short duration, in contrast to the extremely long-lasting inhibition, e.g. by tranylcypromine. Moclobemide only slightly potentiates the pressor effect of oral tyramine in freely moving rats, again in contrast to tranylcypromine; it is not anti-cholinergic and is free of hepatotoxicity. Published evidence on the preclinical pharmacology is reviewed.

The enzyme which metabolises several biogenic amines by oxidative deamination was named monoamine oxidase (MAO) by Zeller (1938); it exists in two catalytically distinguishable forms — MAO-A and MAO-B. The first, MAO-A, prefers 5-hydroxytryptamine (5-HT) and noradrenaline as substrates and is selectively inhibited by clorgyline. The second, MAO-B, preferentially deaminates phenylethylamine and benzylamine, L-deprenyl (selegiline) being a relatively specific inhibitor of this isoenzyme. Tyramine and dopamine, however, are good substrates for both enzyme forms (Johnston, 1968; Yang & Neff, 1974; Fowler & Callingham, 1978; Suzuki *et al*, 1982). The two MAO forms are encoded by two different genes (Bach *et al*, 1988), and differ clearly in their tissue and cellular distribution (for review see Denney & Denney, 1985). This paper summarises some relevant pharmacological properties of the novel, reversible and selective MAO-A inhibitor moclobemide; its main neurochemical properties have been described recently (Burkard *et al*, 1989; Da Prada *et al*, 1989).

History

The modern pharmacotherapy of depression began in the 1950s with iproniazid, an analogue of the tuberculostatic agent isoniazid. At the same time, Zeller *et al* (1952) discovered that iproniazid, in contrast to the tuberculostatic agent isoniazid, was a potent inhibitor of MAO. Iproniazid and other irreversible MAO inhibitors (MAOIs) of the first generation became clinically discredited by reports perpetuating the belief that MAO inhibition is synonymous with severe liver toxicity (Dostert, 1984) and with pronounced orthostatic hypotension (Goldman *et al*, 1986). The prevailing negative attitude was fostered by the occasional occurrence of 'cheese responses', namely hypertensive crises provoked by tyramine ingested with food and no longer deaminated presystemically.

As was the case with iproniazid, the discovery of moclobemide's inhibitory activity on MAO was largely accidental, since it was first synthesised as a potential lipid-lowering agent. A promising anti-lipaemic activity was found within a series of glucosamine derivatives and two of these glucosamine derivatives underwent clinical trials, but their development had to be terminated due to insufficient activity in man. Substitution of the glucosamine moiety by morpholinoethylamine led to Ro 11-1163 (moclobemide; Fig. 1), which was found to be inactive as a lipid-lowering agent. However, its benzamide structure attracted the attention of pharmacologists by virtue of its analogy to known benzamide neuroleptics, such as metoclopramide or sulpiride, which suggested that moclobemide might be a dopamine antagonist.

Accordingly, it was tested in rats for a possible ability to increase dopamine turnover. Instead of the expected increase of homovanillic acid, typically elevated by neuroleptics as a consequence of dopamine receptor blockade, the level of this main dopamine metabolite was significantly decreased by moclobemide.

This unexpected finding pointed to the possibility that moclobemide inhibited MAO, although only three chemical classes of MAOIs were then known — hydrazines and hydrazides, cyclopropylamines, and propargylamines. The inhibitory activity of moclobemide was subsequently confirmed by a variety of methods (Burkard *et al*, 1989; Da Prada *et al*, 1989). The fact that moclobemide produced only a short-lasting (<24 h) inhibition of MAO, in contrast to the classical inhibitors which act for several weeks, indicated a considerable advantage for a possible clinical use. About

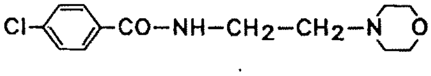

FIG. 1 Chemical structure of moclobemide.

50 analogues of moclobemide were in fact synthesised, but none showed a major advantage over the first compound. Therefore, moclobemide was prepared for clinical trial as a MAO inhibitor.

Main characteristics

This section summarises some of the relevant results of moclobemide which have been described in detail elsewhere (Da Prada *et al*, 1988, 1989; Burkard *et al*, 1989).

Relative high potency *in vivo*

When tested *in vitro* with rat brain homogenates, moclobemide was found to inhibit MAO-A fairly selectively, but with relative low potency. For *in vivo* experiments, the drug was administered orally to rats, 2 h before decapitation. MAO activity was then measured *in vitro* in brain homogenates. Moclobemide was found (Da Prada *et al*, 1989) to inhibit MAO-A preferentially in rat brain, and to be approximately equipotent to tranylcypromine and isocarboxazid, but notably, ten times more potent than phenelzine. Therefore, in spite of its weak MAO-A inhibition *in vitro*, moclobemide *in vivo* is as potent as the MAOIs currently in clinical use (Fig. 2).

Short duration of action

In order to assess the duration of MAO inhibition, moclobemide and reference compounds were administered orally to rats at various times before decapitation, and MAO-A activity in tissue homogenates was measured radiochemically with [^{14}C]5-HT as substrate. For methodological details see Da Prada *et al* (1989). Monoamine oxidase activity is expressed as a percentage of that found in vehicle-treated control rats.

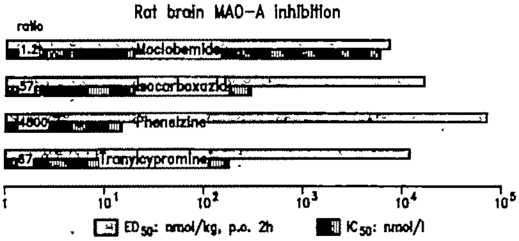

FIG. 2 Comparison of the MAO inhibitory potencies of moclobemide with irreversible, non-selective MAO inhibitors *in vitro* and *ex vivo*. *In vitro* data are expressed as IC$_{50}$ values. For *in vivo* experiments the drugs were administered p.o. 2 h before decapitation and the ED$_{50}$ values calculated from results with various doses. A low ratio (ED$_{50}$/IC$_{50}$) indicates a relatively stronger inhibition *in vivo* than *in vitro*.

In the *in vivo* experiments presented here, the time course of MAO-A inhibition was measured in brain and liver of rats administered 10 mg (37 μmol)/kg moclobemide or an equi-effective dose of tranylcypromine 3 mg (16 μmol)/kg. As shown in Fig. 3, this dose of moclobemide produced peak inhibition by 80% in liver and brain 30 min after drug treatment, and the enzyme activity subsequently recovered completely by 16 h (Da Prada *et al*, 1989). In contrast, the irreversible inhibitor, tranylcypromine, had a somewhat slower onset of action, with maximum inhibition between 4 and 8 h, and only about 50% of the enzyme activity recovered within 48 h. The time-course of MAO-A inhibition was virtually the same in rat whole brain and liver.

Minimal potentiation of tyramine pressor effect

It was particularly important to study the interaction of irreversible and reversible MAOIs with the tyramine pressor effect because of the cheese reaction encountered with the older compounds.

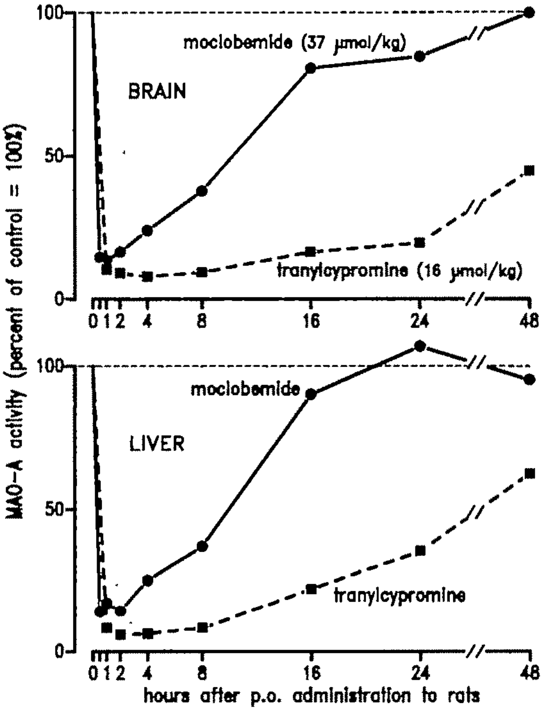

FIG. 3 Time course of MAO-A inhibition in rat brain and liver after moclobemide or tranylcypromine. At time 0, moclobemide (10 mg/kg) or an equipotent dose of tranylcypromine was administered orally to rats and at the times indicated MAO activity was measured in homogenates of whole brain or liver. Mean values of four rats per group are shown. The SEMs (not shown) were <5%.

Mean arterial blood pressure (MAP) was measured directly in freely moving rats fitted with an indwelling catheter in a carotid artery (Carruba *et al*, 1981). The irreversible MAOI, tranylcypromine, was found to increase the sensitivity to oral tyramine much more drastically than moclobemide. From Fig. 4A it can be seen that a subthreshold dose of tyramine (5 mg/kg p.o.), given as a bolus, produced no blood pressure increase in rats treated with 30 mg/kg of moclobemide orally (Da Prada *et al*, 1988). However, the same dose of tyramine led to a rise of about 35 mmHg after 6 mg/kg of tranylcypromine. Inhibition of liver MAO-A was about 90% with both compounds. By comparison of the area under the curves, it was calculated that tranylcypromine produces a 12-fold greater potentiation of the tyramine pressor effect than moclobemide. These values are in full agreement with results obtained in human volunteers (Korn *et al*, 1988*a*,*b*).

The *intravenous tyramine test* is frequently used in clinical trials to assess the function of the peripheral noradrenergic system and its response to drugs such as MAOIs (Ghose, 1984). The test was criticised because it does not simulate the actual clinical situation (Simpson & White, 1984), where this amine is ingested in the form of tyramine-rich food or beverages and is exposed to high intestinal and hepatic MAO activity before reaching the systemic circulation.

The following experiments (Fig. 4B) show that the two MAOIs, moclobemide and tranylcypromine, induce about the same potentiation of the pressor response to intravenous tyramine, suggesting that a similar degree of MAO inhibition in and around noradrenergic nerve endings is achieved by both reversible and irreversible inhibitors. The reason for this lack of difference between the two types of MAOIs in this situation may be that minute amounts of tyramine injected as an intravenous bolus easily penetrate the capillary wall because of the marked inhibition of MAO in the endothelial cells, which is almost exclusively of the MAO-A type (Youdim *et al*, 1984). Therefore, tyramine is very transiently accumulated in noradrenergic nerve endings in concentrations sufficient to release noradrenaline, but for too short a period of time to displace the reversible inhibitor from the enzyme (Da Prada *et al*, 1984; Keller *et al*, 1987). Tyramine administered p.o., however, reaches the systemic circulation very slowly, and the protracted exposure to presystemic MAO (in the gut and liver) may partially overcome the reversible inhibition by moclobemide.

Systemic studies in humans using either intravenous (Tiller *et al*; 1987; Korn *et al*, 1988*a*,*b*) or oral administration of tyramine (Simpson & White, 1984; Bieck & Antonin, 1988; Korn *et al* 1988*a*) have shown that after moclobemide a threshold blood pressure rise required approximately 100 mg tyramine orally. Moreover, the pressor response to this high dose of tyramine was considerably smaller when tyramine was given with a solid meal to simulate the real-life situation.

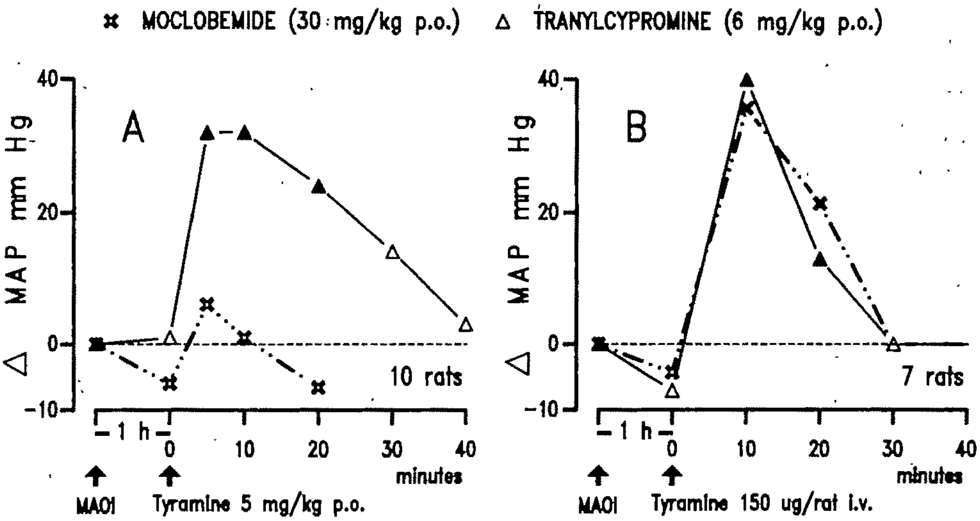

FIG. 4 Effect of moclobemide and tranylcypromine on the blood pressure increase induced by tyramine administered by different routes. Tyramine was administered either orally (A) or intravenously (B) in chronically cannulated rats 1 h after oral administration of the MAO inhibitors. At the doses used, tyramine alone did not change mean arterial blood pressure (MAP) in untreated control rats. Pre-drug values of MAP ranged from 110 to 130 mmHg. Closed symbols indicate values significantly different from baseline.

It is relevant that most foods and beverages analysed recently (Da Prada *et al*, 1988) contain considerably less tyramine than reported previously, and that the total amount of tyramine contained in a copious five-course meal does not exceed 40 mg. The results of the oral tyramine test in humans yield the important information that amounts below 100 mg are highly unlikely to elicit a relevant rise of blood pressure in subjects treated with moclobemide (see also Cooper, this supplement).

Lack of hepatotoxicity

Toxic liver reactions to MAOIs have been documented in only a few cases and only with iproniazid and pheniprazine (Dostert, 1984). In a rat model for liver toxicity, iproniazid given after phenobarbitone pretreatment, produced distinct hepatotoxic effects, while moclobemide did not. The hepatotoxicity of iproniazid was most impressive in histopathological examination, where marked liver necrosis was apparent. In contrast to irreversible MAOIs of the hydrazine type, moclobemide is completely devoid of hepatotoxicity (Schläppi, 1985).

Conclusion

The results taken into consideration in this paper clearly demonstrate the short duration of action of moclobemide on MAO in contrast to the much longer-lasting inhibition induced by the irreversible MAOI tranylcypromine. Due to its chemical structure, the reversible MAO-A inhibitor, moclobemide, cannot be converted into isopropyl hydrazine — the hepatotoxic molecule suspected to induce liver necrosis after iproniazid (Timbell, 1979). Many investigations, both preclinical and clinical, have shown that moclobemide only very weakly potentiates the pressor effect of orally-administered tyramine, which virtually eliminates the risk of severe hypertensive crises (cheese effect) in therapeutic use. Moclobemide is thus likely to make a useful contribution to the treatment of depressive disorders due to its well-documented safety characteristics, its lack of anticholinergic effects, and its good tolerability.

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Contents

List of Contributors 4

Introduction
D. ECCLESTON 5

Evidence for the 5-HT hypothesis of suicide: A review of post-mortem studies
J. J. MANN, V. ARANGO, P. M. MARZUK, S. THECCANAT and D. J. REIS 7

Obsessive–compulsive disorder as a 5-HT subsystem-related behavioural disorder
D. L. MURPHY, J. ZOHAR, C. BENKELFAT, M. T. PATO, T. A. PIGOTT and T. R. INSEL 15

Serotonergic dysfunction in depression
H. MELTZER 25

The antidepressant effects of 5-HT uptake inhibitors
A. ÅBERG-WISTEDT 32

Reduction of food intake by manipulation of central serotonin: Current experimental results
S. GARATTINI, T. MENNINI and R. SAMANIN 41

Central serotonin and impulsive aggression
E. F. COCCARO 52

Is there a relationship between serotonin receptor subtypes and selectivity of response in specific psychiatric illnesses?
S. H. MONTGOMERY and N. FINEBERG 63

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Introduction

DONALD ECCLESTON

It is now over 30 years since Gaddum & Picarelli (1957) described and characterised tryptamine receptors in the periphery. The setting in which they were working was what to us now is an antique department of pharmacology whose most sophisticated equipment was a smoked drum to record the response of a variety of smooth muscle preparations to the extracts of tissue containing the sought after transmitters. Gaddum the Professor of Pharmacology was the ideas man, Crawford a brilliant though highly obsessional methodologist, and Amin an indefatigable Indian PhD student. That group (Amin *et al*, 1954) described the presence of 5-HT in brain. They had been looking for substance P but the contractile response of the preparations to the extracts of brain did not resemble that peptide but serotonin. In many ways that was an initiator of psychopharmacology which has progressed exponentially to the present day.

The 5-HT system of neurones in brain originally seen as rather primitive has emerged with great complexity especially in relation to its receptor population. It now appears that the M and D receptors they described are indeed now characterised as 5-HT_3 and 5-HT_2. Indeed the wide range of 5-HT receptors currently characterised (Tricklebank, 1987) would have surprised Gaddum himself; 5-HT has also been implicated in many diverse behaviours as well as the control of mood. It is difficult to see the common themes in obsessional behaviour, suicidal intent, bulimia, aggression, anxiety and appetite. The facilitation or inhibition of the repetition of specific behaviours might, however, as in for example, obsessive compulsive neurosis or bulimia, be one of these and lead to some understanding of the drugs currently available to the psychiatrist. Although the drugs discussed at this symposium are themselves highly specific in blocking the reuptake of 5-HT into the neurone; their efforts may be non-specific since they will depend on the increased concentration of the amine caused by reuptake inhibition at particular groups of receptors entering into play as the intrasynaptic and extrasynaptic level of 5-HT rises.

What is also becoming apparent is the potential for different doses of these drugs to have different effects. Low doses of clomipramine appear to be efficacious in panic disorder with a rapid onset whilst higher doses for a longer period appear to be necessary for the treatment of depression. This may, of course, reflect the concentration of 5-HT at receptor sites whose sensitivities to this amine differ. Long continued use of specific 5-HT reuptake inhibitors to cause down regulation of 5-HT_2 receptors may be necessary in the treatment of depression. These questions are addressed on a broad front in this symposium and are beginning to suggest answers to difficult clinical problems.

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Evidence for the 5-HT Hypothesis of Suicide

A Review of Post-mortem Studies

J. J. MANN, V. ARANGO, P. M. MARZUK, S. THECCANAT and D. J. REIS

Although suicide was traditionally considered an extreme response to stress, with the most frequent stress being depressive illness, severity of depression does not distinguish those who commit suicide from non-suicide attempters. A biological role involving the serotonergic system, possibly associated with a genetic risk factor, has been postulated. Low levels of 5-HT and 5-HIAA have been found in post-mortem examinations of brain-stem tissues of suicide victims (levels in cortical tissue were generally normal). An increased number of 5-HT_2 receptors was found in the pre-frontal cortex of suicide victims, such upregulation having been demonstrated in induced 5-HT deficiency states; 5-HT_{1A} receptors were also increased. Receptor populations may be altered by chronic psychotropic medication; e.g. 5-HT_2 downregulation occurs following administration of antidepressants. There is some indication that the adrenergic system may be involved as well, but this will require further study. Antidepressant drugs may be effective in preventing suicide in patients with non-depressive syndromes who exhibit suicidal behaviour.

Suicide was traditionally considered to be an extreme response to stress, and the most frequent stress associated with suicide is a major depressive illness (Pokorny, 1983). However, severity of depression does not seem to distinguish those who commit suicide from non-suicide attempters among patients with major depression (Beck *et al*, 1985). Moreover, only a small percentage of depressed patients actually commit suicide during an index episode of illness. Other factors, therefore, must play an important role in determining whether suicide is part of the response to a stress such as depressive illness.

Recently, two lines of convergent evidence have emerged to suggest a biological contribution to the risk for suicide. The first is the presence of a genetic risk factor (Roy, 1986) and the second is the finding of a number of biological correlates of suicidal behaviour (Mann & Stanley, 1984). Some of the latter may ultimately prove to be related to the genetic risk factor, but at this stage it is not known which biological correlates are state- or trait-dependent.

This review will focus on the relationship of the serotonergic system to suicide as revealed by studies of human post-mortem brain tissue while making brief reference to parallel studies of suicide attempters in order to compare findings. Although most studies of biological correlates of suicidal behaviour have examined the 5-HT (serotonin) system, that does not mean other transmitter systems are not involved. It should be emphasised that since the 5-HT system appears to be involved in impulsive aggression in general (Brown *et al*, 1982*a*,*b*) and not just the specific subtype of aggressive behaviour represented by suicide, other transmitter systems probably determine whether the aggression is directed inwards, in the form of suicide, or outwards, as assault or homicide.

Originally, post-mortem neurochemical assessment of monoamine neurons involved the measurement of absolute levels of amines and their metabolites. However, those indices provide only limited information as to the functional status of those systems. Post-mortem delay, the agonal process, drugs, age, gender, and seasonal and diurnal effects may all influence amine levels (Spokes, 1979; Carlsson *et al*, 1980; Allen *et al*, 1983; Mann *et al*, 1984). The absolute levels of a transmitter do not distinguish between the biogenic amine in low-turnover storage pools and amine content immediately available for release and transmission. The ratio of metabolite to amine level may be a better guide to functional activity. Two alternative approaches that have been employed to assess neuronal activity are the measurement of receptor binding indices and the assay of biosynthetic enzyme activity (Creese *et al*, 1976; Reis *et al*, 1977). The latter approach has rarely been applied in suicide research. Therefore, this paper will focus on the application of receptor binding methodology to the area of post-mortem brain research in suicide and will emphasise the serotonergic system, which has been implicated in the pathogenesis of suicidal behaviour by a variety of studies of suicide attempters and completers (see Mann & Stanley, 1986, for a review).

Post-mortem studies of pre-synaptic serotonergic indices in suicide

Levels of 5-HT and 5-hydroxyindoleacetic acid

Initial post-mortem neurochemical studies in psychiatric patients measured levels of 5-HT and/or 5-hydroxyindoleacetic acid (5-HIAA) in the brain-stem of suicide victims as a way of studying the biochemistry of depressive illness. The results are shown in Table I. Some, but not all, studies reported modestly lower levels of 5-HIAA and/or 5-HT in brain-stem regions of suicide victims but generally normal levels in cortical tissue.

On closer examination it is apparent that many of the suicides were not the result of a depressive illness but were associated with other diagnoses (Shaw *et al*, 1967; Bourne *et al*, 1968; Pare *et al*, 1969; Lloyd *et al*, 1974; Beskow *et al*, 1976). Nevertheless, the reduction in brain-stem levels of 5-HT or 5-HIAA was independent of the specific psychiatric diagnosis and therefore appeared to correlate with suicidal behaviour (see Table II). That conclusion is consistent with the finding of low levels of 5-HIAA in the cerebrospinal fluid (CSF) of those who attempt suicide by violent means (Ågren, 1980; Träskman *et al*, 1981; Brown *et al*, 1982*a,b*; van Praag, 1983).

In general, those studies indicate the presence of lower levels of 5-HIAA in the cerebrospinal fluid of attempters versus non-attempters who were matched for diagnosis. Such observations have been made in several diagnostic groups, including patients with a major depressive disorder (Träskman *et al*, 1981) and personality disorders without a major depressive episode (Träskman-Bendz *et al*, 1986; Brown *et al*, 1982*a,b*). Most, but not all, studies in schizophrenia (van Praag, 1983; Ninan *et al*, 1984) show the same results. Several investigations of bipolar patients have failed to demonstrate decreased levels of 5-HIAA in the cerebrospinal fluid of attempters when compared with non-attempters. The explanation may lie in the observation that a decreased level of

TABLE I

Levels of serotonin and 5-hydroxytryptamine in post-mortem brain tissue from suicide victims versus controls

	Brain stem		*Frontal cortex*		*Other regions*	
Study	*5-HT*	*5-HIAA*	*5-HT*	*5-HIAA*	*5-HT*	*5-HIAA*
Pare *et al* (1969)	↓11%*	nc[1] (↓13%)	—	—	—	—
Shaw *et al* (1967)	↓11%*	—	—	—	—	—
Lloyd *et al* (1974)	↓29%*	nc	—	—	nc	nc
Bourne *et al* (1968)	nc	↓28%*	—	—	—	—
Beskow *et al* (1976)	—	↓26%*	nc	↓43%*	nc	↓18%*
Cochran *et al* (1976)	nc	—	nc	—	nc	—
Stanley *et al* (1986)	—	—	nc	nc	—	—
Owen *et al* (1986)	—	—	—	—	nc	nc or ↑27%[2]
Owen *et al (1983)*	—	—	—	↓28%	—	—
Korpi *et al* (1986)	nc	nc	nc	nc	↓50%*[3]	—
Arató *et al* (1987)	—	—	nc	nc	—	—
Crow *et al* (1984)	—	—	—	↓25%[4]	—	—

* Indicates a statistically significant difference.

nc = no change.

1. Greater assay variance in the control group and half the sample size may have contributed to the lack of statistical significance for the difference in 5-HIAA levels.
2. Increase in hippocampus; no change in occipital cortex.
3. Reduction in 5-HT was confined to non-schizophrenic suicides (hypothalamus).
4. ↓35% in depressed suicides, but neither decrease was statistically significant.

TABLE II

Post-mortem levels of serotonin and 5-hyroxyindoleacetic acid in the brain of suicide victims and controls: a comparison across diagnostic subgroups

Study		*Diagnostic subgroup and percentage decrease in 5-HT or 5-HIAA*
Pare *et al* (1969)	5-HT	Melancholia 9% MDD (non-melancholia) 20%↓
Shaw *et al* (1967)	5-HT	MDD 19%↓ schizophrenia 12%↓ alcoholism 22%↓
Bourne *et al* (1968)	5-HT	Depressed suicides 3%↓ non-depressed suicides 0%↓
	5-HIAA	Depressed suicides 30%↓ non-depressed suicides 23%↓
Korpi *et al* (1986)	5-HT	Non-schizophrenics 50%↓
Cochran *et al* (1976)	5-HT	Depressed suicides 33%↓ alcoholic suicides 17%↓

5-HIAA in the cerebrospinal fluid is already associated with bipolar disorder, and any further decrease associated with suicide risk is less easily demonstrated.

Studies of the imipramine binding site

The development in the late 1970s of methods to assay reliably neurotransmitter receptors in post-mortem brain tissue offered a new approach for examining the question of aminergic function in suicide. The most informative pre-synaptic marker for the serotonergic system is the imipramine binding site. This receptor is thought to be located on 5-HT nerve terminals and is associated with the 5-HT transporter (Paul *et al*, 1984; Langer *et al*, 1987; Laruelle *et al*, 1988). Thus, the imipramine binding site is an index of the number and/or functional status of the 5-HT nerve terminals. The initial report by Stanley *et al* (1982) of fewer imipramine binding sites in the pre-frontal cortex of suicide victims when compared to matched controls was of great interest as it suggested impaired pre-synaptic serotonergic function. However, a number of subsequent studies, but not all, have cofirmed that finding (see Table III). One explanation for the lack of total agreement may be that imipramine is a non-specific ligand with high affinity for muscarinic cholinergic and alpha-adrenergic receptors amongst others. Changes in those other receptor populations, therefore, will influence the results. Other explanations include the drugs present ante-mortem, technical differences in brain collection, dissection, and assay; the presence of other psychiatric diagnoses; and methods of suicide.

The importance of regional differences in neurochemical correlates of suicide is highlighted by Gross-Isseroff *et al* (1989), who studied the brains of suicide victims. They reported [^{3}H]-imipramine binding was elevated in some brain regions, such as the pyramidal and molecular layers of the hippocampus, and decreased in others, such as the post-central gyrus and insula.

It is of note that two studies (Paul *et al*, Gross-Isseroff *et al*, 1988) found normal levels of [^{3}H]-desipramine in the brains of suicide victims. In contrast to imipramine binding sites, which are located on 5-HT nerve terminals, [^{3}H]-desipramine is an index of noradrenergic nerve terminals because it binds to the norepinephrine transporter. Thus, the alteration in [^{3}H]-imipramine binding does not appear to generalise to noradrenergic nerve terminals.

5-HT Receptor binding studies in suicide

Some animal studies have shown that destruction of the serotonergic neurons at the level of the raphe nuclei by chemical or electrolytical methods or depletion of 5-HT by tetrabenazine increases the number of, or upregulates, post-synaptic 5-HT$_2$ binding sites (Brunello *et al*, 1982; Takahashi *et al*, 1982; Roth *et al*, 1987) and decreases imipramine binding and 5-HT uptake. Conversely, increasing intrasynaptic levels of 5-HT by chronic administration of 5-HT reuptake inhibitors reduces the number of, or downregulates, 5-HT$_2$ binding sites (Peroutka & Snyder, 1980; Stanley & Mann, 1984). Those sites are also labelled by 5-HT antagonist drugs such as mianserin and ketanserin as well as many antipsychotics, including spiroperidol and haloperidol (Roth *et al*, 1987); 5-HT$_1$ receptors are not

TABLE III

Post-mortem imipramine binding receptor studies of suicide victims

Study	*Frontal cortex*	*Other regions*
Stanley *et al* (1982)	↓44%*	—
Paul *et al* (1984)[1]	—	↓30%*
Crow *et al* (1984)[2]	↓19%	—
Meyerson *et al* (1982) (all violent)	↑35%	—
Meltzer *et al* (1987)	nc	—
Owen *et al* (1986)	nc	nc
Gross-Isseroff *et al* (1988)	nc	↑*and↓*
Arató *et al* (1987)[3]	↓48%*↑153%*	nc

* Indicates a statistically significant difference.

nc = no change.

1. The two studies found normal levels of [^{3}H]-desipramine binding in the suicide group.
2. The significant decrease in IMI binding was confined to a subgroup of suicides with a depressive disorder.
3. Suicides have lower binding on right side and higher binding on left side compared to controls.

affected by such manipulations (Wirz-Justice *et al*, 1978).

We reported an increased number of 5-HT_2 receptors in the pre-frontal cortex of suicide victims (Stanley & Mann, 1983; Mann *et al*, 1986), and we have now demonstrated that finding in three separate series of violent suicide victims who were compared to matched controls. Three subsequent studies by other laboratories (shown in Table IV) have replicated our findings (Ferrier *et al*, 1986; Owen *et al*, 1983; Meltzer *et al*, 1987), although two studies (Owen *et al*, 1986; Cheetham *et al*, 1988) did not. Many of the subjects in the study conducted by Cheetham *et al* (1988) had been receiving tricyclic antidepressants, and the finding of an elevated equilibrium dissociation constant, K_d, for 5-HT_2 receptors in the suicide group compared to controls suggests the presence of 5-HT_2 antagonists and other psychotropic drugs in the suicide group. The effects of such drugs as well as other factors discussed below could explain the discrepant results.

The biochemical specificity of those changes within the 5-HT system is indicated by our observation that [^{3}H]-5-HT binding was not altered in suicide brains (Mann *et al*, 1986). More recently, Meltzer (1988) found that the 5-HT_{1A} subpopulation of these [^{3}H]-5-HT receptors was indeed increased in suicide brains. Further systematic study of the 5-HT_{1A}, 5-HT_{1C}, and 5-HT_{1D} receptors would therefore be of considerable interest. We and others have determined that 5-HT_{1B} receptors appear not to be present in the human brain.

Effect of associated psychiatric diagnosis on neurochemical findings in suicide

Most studies of suicide victims have involved a mixture of diagnoses (Table II). In those studies for which data are available, a reduction in 5-HT or 5-HIAA does not appear to be associated with a specific psychiatric syndrome such as melancholia. Reductions equivalent to those seen in melancholics have been found in every study of persons diagnosed with non-melancholic depression, just as in cases not diagnosed as Major Depressive Disorder (MDD) when compared with MDD cases (see Table II). Those results are consistent with studies of 5-HIAA levels in cerebrospinal fluid, which have found lower levels of 5-HIAA in suicide attempters suffering from personality disorders (Brown *et al*, 1982*a,b*; Träskman-Bendz *et al*, 1986) and schizophrenia (van Praag, 1983) and in patients with MDD (Träskman *et al*, 1981) who were compared with non-attempters with the same diagnosis and severity of depression.

Ferrier *et al* (1986), and the same group in a more recent report (Yates *et al*, 1988), found an increase in 5-HT_2 binding in the pre-frontal cortex of depressed patients dying from natural causes. Their findings suggest that part of the change in serotonergic indices may reflect the presence of MDD. It is not known how changes in 5-HT_2 binding and imipramine binding differ during the immediate ante-mortem period in suicides with and without MDD. If a difference exists, it may explain some of the disagreement in the literature as to the origin of altered 5-HT indices in the brain of suicide victims, such indices being complicated by the variation between studies in the proportion of patients with unmedicated MDD.

Effects of psychotropic medications on 5-HT receptors

The use of antidepressants and antipsychotics can be a critical factor in determining whether serotonin function changes occur in cases of suicide and MDD. Chronic,

TABLE IV

Post-mortem 5-HT_2 receptor binding studies in the brain of suicide victims

Study	*Pre-frontal cortex (PFC)*	*Other areas*
Stanley & Mann (1983)	↑44%*	—
Mann *et al* (1986)	↑28%*	—
Meltzer *et al* (1987)	↑	—
Owen *et al* (1986)	nc	nc
Cheetham *et al* (1988)[1]	nc	nc
Depressed non-suicides		
Ferrier *et al* (1986)	↑36%	—
Yates *et al* (1988)[2]	↑71%*	

* Indicates a statistically significant difference

nc = no change.

1. Violent suicides compared to non-violent suicides showed more binding sites in PFC (15%) and amygdala (19%) but differences were not statistically significant.
2. Depressed subjects dying from causes other than suicide.

but not acute, administration of antidepressants to rodents downregulates 5-HT_2 receptors (Peroutka & Snyder, 1980). Recently, Yates *et al* (1988) reported 5-HT_2 binding was elevated in the pre-frontal cortex of untreated patients with MDD but was normal in patients taking tricyclics. Their findings suggest downregulation (or reduction of binding from abnormally high to normal levels) of 5-HT_2 receptors may occur in the human brain in the same way as has been reported in rodent studies (Peroutka & Synder, 1980). Antipsychotics are usually 5-HT_2 antagonists as well as dopamine receptor antagonists, and as a result they may cause competitive inhibition of binding to 5-HT_2 receptors that would be reflected in an increase in the equilibrium dissociation constant, K_d, as was seen in the suicide group in the report of Cheetham *et al* (1988).

Violence of suicide attempt, aggression, and serotonergic studies

Based on studies of 5-HIAA levels in cerebrospinal fluid (Ågren, 1980; Träskman *et al*, 1981), the reduction in serotonergic activity appears to correlate positively with the degree of violence of the suicide attempt. An examination of post-mortem studies from this perspective is shown in Table V. It is clear that the currently available data on the relationship between the violence of the suicide attempt and the biochemical indices studied are insufficient to draw firm conclusions. Investigators generally did not address this question. However, the data in Table V suggest the degree of violence of suicide method appears to be unrelated to the presence of lower levels of 5-HT or 5-HIAA. Receptor studies suggest violent attempters have increased 5-HT_2 receptor binding (Stanley & Mann, 1983; Mann *et al*, 1986; Meltzer *et al*, 1987), and populations with a significant proportion of non-violent attempters show no such changes (Owen *et al*, 1986; Cheetham *et al*, 1988; Meltzer *et al*, 1987). This issue merits further study.

An association has been reported between aggressive or impulsive behaviour and a low level of 5-HIAA in the cerebrospinal fluid (Brown *et al*, 1982*a,b*), but no formal studies of such a relationship have been carried out in post-mortem brain tissue of suicide victims. Thus, lowered levels of serotonergic activity may contribute to the violent or impulsive aspects of suicidal behaviour. It is not clear why such behaviour is inwardly directed in some individuals, taking the form of suicidal acts, and outwardly directed in others and expressed as aggression towards other individuals. Coexistent changes in other neurotransmitter systems such as the noradrenergic or dopaminergic systems may determine the direction of the violent impulsive act. For example, our post-mortem findings suggest the presence of reduced noradrenergic activity in suicide victims. Research in other laboratories has suggested an association of increased noradrenergic activity and aggression. This two-transmitter hypothesis has profound theoretical and treatment implications and demands urgent study.

Neurochemical specificity of correlates of suicidal behaviour

The biochemical selectivity or specificity of the post-mortem neurochemical correlates of suicide remain to be established. To date, most work has concentrated on the serotonergic system. A confluence of post-mortem studies (Bourne *et al*, 1968; Mann & Stanley, 1986; Mann *et al*, 1986), cerebrospinal fluid studies (Ågren,

TABLE V

Percentage of violent suicides in post-mortem brain studies assessing levels of 5-HT and 5-HIAA

	Percentage of violent suicides
I. Studies finding a significant decrease in 5-HT or 5-HIAA in suicide victims	
1. Pare *et al* (1969)	0
2. Shaw *et al* (1967)	14
3. Beskow *et al* (1976)	48
4. Bourne *et al* (1968)	9
5. Korpi *et al* (1986)	60
6. Lloyd *et al* (1974)	50
II. Studies finding no significant decrease in 5-HT or 5-HIAA in suicide victims	
1. Cochran *et al* (1976)	84
2. Arató *et al* (1987)	0
3. Crow *et al* (1984)	44

1980; Träskman *et al*, 1981; Brown *et al*, 1982*a,b*; van Praag, 1983), and neuroendocrine challenge tests (Meltzer *et al*, 1984) has pointed towards an association between reduced serotonergic activity and suicidal behaviour. However, other investigators, including those in our own laboratory, have reported alterations in indices of adrenergic function in suicide victims, such as increased beta-adrenergic binding in the pre-frontal cortex (Mann *et al*, 1986; Biegon & Israeli, 1988). Those data suggest involvement of the noradrenergic system. In contrast, no differences in cholinergic binding in the frontal cortex of suicide victims have been found (Stanley, 1984; Gillin *et al*, 1986), suggesting the cholinergic system may be spared. Clearly, more complete studies are necessary, because cholinergic muscarinic binding does not appear to be altered in the presence of Alzheimer's disease, where degeneration of cholinergic neurons and loss of choline acetyltransferase activity has been demonstrated.

An increased number of corticotropin releasing hormone receptors have been reported in cortical tissue of suicide victims (Nemeroff *et al*, 1988). That finding has been interpreted to be consistent with the hypothalamic–pituitary–adrenal axis hyperactivity seen in depressive illness. Preliminary evidence also exists for an increase in benzodiazepine binding in the frontal cortex (Cheetham *et al*, 1988) and hippocampus (Manchon *et al*, 1987). Whether those changes are primary or secondary remains to be determined.

Treatment Implications

Antidepressants produce effects that are the opposite of the alterations found in the same monoaminergic receptor populations in suicide victims, namely the 5-HT_2 and the beta-adrenergic receptors (Stanley & Mann, 1984). It is therefore reasonable to hypothesise that the effect of antidepressants may account for both the *antidepressant* and *antisuicidal* action of those compounds. Since suicidal behaviour is found in syndromes unrelated to depression, antidepressant drugs might be effective for the suicidal component of such psychiatric syndromes.

Summary

The results of post-mortem receptor binding studies of the brains of suicide victims are consistent with a state of reduced serotonergic activity in suicide victims (fewer pre-synaptic [^{3}H]-imipramine receptors and an increased number of 5-HT_2 post-synaptic receptors). Those exciting preliminary findings suggest post-mortem receptor binding studies are a very promising and informative approach for assessing monoaminergic function in the central nervous system. Future work will focus on the localisation within the brain of the changes in the serotonergic system and their relationship to the method of suicide, associated psychiatric disorders, and changes in other transmitter systems.

More neurotransmitter systems must be studied to determine the *neurochemical specificity* of the changes associated with suicidal behaviour. The combination of pre-synaptic and post-synaptic measures may assist in localising the reason for altered neural transmission to the pre-synaptic or post-synaptic region.

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Obsessive–Compulsive Disorder as a 5-HT Subsystem-Related Behavioural Disorder

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Involvement of the brain serotonin (5-HT) neurotransmitter system in obsessive–compulsive disorder (OCD) was originally suggested on the basis of therapeutic effects found with the semi-selective serotonin uptake inhibitor, clomipramine. More recent studies directly comparing clomipramine with non-selective or norepinephrine-selective uptake inhibitors, such as desipramine or nortriptyline, as well as studies with new, more selective serotonin uptake inhibitors, including fluvoxamine and fluoxetine, have supported that hypothesis. Clomipramine's antiobsessional effect has been augmented with the serotonin precursor, L-tryptophan, or with lithium, which has prominent serotonergic effects. Patients whose OCD symptoms improved on clomipramine worsened when the drug was discontinued (regardless of duration of therapy) and improved when clomipramine was reinstituted. OCD symptoms also worsened when metergoline, a 5-HT antagonist, was given to patients who had improved with clomipramine. Metergoline given alone had no effect. Administration of *m*-chlorophenylpiperazine (*m*-CPP), a 5-HT receptor agonist, to untreated OCD patients increased their anxiety, depression, and dysphoria, and exacerbated their OC symptoms. After 4 months of clomipramine therapy, *m*-CPP failed to produce the same behavioural effects, suggesting an alteration of a 5-HT subsystem (possibly downregulation of some 5-HT receptors). The data reviewed suggest an important role for an abnormal brain 5-HT subsystem in patients with OCD.

Among the many psychiatric syndromes that have been linked to brain 5-hydroxytryptamine (5-HT, or serotonin) function, obsessive–compulsive disorder (OCD) can be regarded at the present time as the dysfunction with the most compelling evidence to support a 5-HT connection. This paper will review and re-evaluate several recent studies conducted by our research group that have provided substantial additional information implicating a brain 5-HT subsystem in this disorder. These studies will be considered in the context of earlier drug treatment studies of OCD, which first suggested that 5-HT function was of importance in the disorder, and recent psychobiological studies of OCD patients.

Treatment studies using 5-HT-selective agents

The suggestion from open studies that the tricyclic antidepressant, clomipramine, had beneficial effects on obsessions in depressed patients and on overall symptomatology in OCD patients can now be regarded as the initiation of a 5-HT hypothesis of OCD (Fernández Córdoba & López-Ibor Aliño, 1967; for reviews, see Insel & Murphy, 1981; Insel *et al*, 1985; López-Ibor, 1988; Zak *et al* 1988). Clomipramine is unique among the tricyclics in its effectiveness as an inhibitor of 5-HT uptake into brain synaptic terminals. As outlined in Table I, some tricyclics, such as nortriptyline and desipramine, are norepinephrine-selective inhibitors, whereas imipramine, amitriptyline, and others are relatively non-selective drugs (Hyttel & Larsen, 1985; Frazer & Brunswick, 1989). The notion that 5-HT might be involved in the treatment effects of clomipramine received support from a small, open study that suggested the 5-HT precursor, L-tryptophan, also was of benefit in OCD patients (Yaryura-Tobias & Bhagavan, 1977), although no placebo-controlled studies with L-tryptophan were ever completed.

Several double-blind studies of the use of clomipramine in well characterised OCD patients that were conducted in the early 1980s provided substantial scientific footing for both the efficacy of drug treatment in this previously treatment-resistant disorder and also for an involvement of changes in 5-HT in clomipramine-responsive patients. The comparative efficacy results from these studies are summarised in Table II. Some of the studies involved comparisons of clomipramine with other tricyclic antidepressants, including nortriptyline, amitriptyline, and imipramine. The evidence that clomipramine was generally more effective than the other tricyclics was interpreted as possibly implicating a 5-HT-dependent process in the therapeutic efficacy of clomipramine. Other studies with small numbers of patients or with short treatment periods did not demonstrate therapeutic effects of clomipramine or of another 5-HT-selective uptake inhibitor, zimelidine. Even the larger studies summarised in Table I had diagnostic, experimental design and limitations with

TABLE I
Effects of various antidepressants on serotonin versus norepinephrine uptake in rodent brain preparations

	IC_{50} values (nmol) Norepinephrine	*Serotonin*	*Ratio NE: 5-HT*
Tricyclic antidepressants			
Clomipramine[1]	24	2	12.0
Amitriptyline[2]	50	150	0.3
Imipramine[2]	30	150	0.2
Nortriptyline[2]	10	600	0.002
Desipramine[2]	2	800	0.002
Serotonin-selective antidepressants			
Fluvoxamine[1]	620	4	151
Fluoxetine[2]	500	15	33
Trazodone[2]	20 000	750	27

1. Adapted from Hyttel & Larsen (1985).
2. Adapted from Frazer & Brunswick (1989).

TABLE II
Controlled comparisons of clomipramine (CMI) in patients with obsessive–compulsive disorder

Result	*Dose (mg/day)*	*Design, n*	*Reference*
CMI v. *placebo* (P)			
CMI > P	150	Parallel, 35	Thorén *et al* (1980*a*)
CMI > P	183	Parallel, 40 (4-week self-rating only)	Marks *et al* (1980)
CMI > P	75	Parallel, 14	Montgomery (1980)
CMI > P	141	Cross-over, 19	Flament *et al* (1985)
CMI > P	229	Parallel, 15	Mavissakalian *et al* (1985)
CMI v. *other antidepressants*			
CMI = nortriptyline (NT) NT response = P response	150, 150	Parallel, 35	Thorén *et al* (1980*a*)
CMI > baseline (B) Amitriptyline response = B	133, 197	Parallel, 20	Ananth *et al* (1981)
CMI > clorgyline	236, 28	Cross-over, 13	Insel *et al* (1983)
CMI > imipramine	275, 265	Parallel, 16	Volavka *et al* (1985)

regard to assessment of change, which, as reviewed elsewhere, render interpretation difficult (Rapoport *et al*, 1980; Prasad, 1984, 1985; Insel *et al*, 1985; Liebowitz *et al*, 1988; Zak *et al*, 1988).

Nonetheless, the hypothesis that 5-HT is involved was supported in particular by statistically significant correlations between therapeutic improvement and the magnitude of reductions in concentrations of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (Thorén *et al*, 1980*b*). A similarly significant correlation between plasma clomipramine levels — but not levels of desmethylclomipramine (DCMI) or other clomipramine metabolites — and clinical response found in two studies (Stern *et al*, 1980; Insel *et al*, 1983) was considered supporting evidence, since DCMI inhibits norepinephrine as well as 5-HT uptake. Additional substantiating data came from correlations of therapeutic responses with changes in platelet 5-HT concentrations, which were found markedly reduced during clomipramine treatment (Flament *et al*, 1987). Other studies, however, did not find equivalent associations between therapeutic response and clomipramine plasma levels (Thorén *et al*, 1980*b*; Flament *et al*, 1987). In any case, correlation studies of this type can provide only suggestive, not conclusive, evidence.

Two recent double-blind studies in OCD were designed to assess more directly serotonergic involvement in therapeutic responses in OCD patients (Zohar & Insel, 1987; Leonard *et al*, 1988). The studies, which used clomipramine, employed the tricyclic antidepressant drug, desipramine, for comparative purposes. The latter agent was chosen because it has low 5-HT uptake-inhibiting effects and low anticholinergic effects (another contrasting property, as clomipramine is strongly anticholinergic) and is a norepinephrine-selective uptake inhibitor. As indicated in Table III, these two studies showed conclusively that clomipramine had significantly greater therapeutic effects than desipramine in OCD patients.

An augmentation of clomipramine's antiobsessional effect has been found for patients with minimal or partial responses to clomipramine by treating them with L-tryptophan (Rasmussen, 1984) or with lithium (Stern & Jenike, 1983; Rasmussen, 1984; Eisenberg & Asnis, 1985). Lithium has been found to enhance serotonergically mediated responses in many clinical and pre-clinical studies, including some that involved pre-treatment with tricyclic antidepressants (Blier & De Montigny, 1985; Price *et al*, 1989).

As the data concerning clomipramine's efficacy in OCD have expanded, it seemed important to determine how long clomipramine treatment needed to be maintained since, conceivably, improvement might reflect a new stabilised state not requiring continuing effects of the drug. To examine the appropriate duration of treatment with clomipramine, we carried out a prospective, placebo-controlled, double-blind discontinuation study (Pato *et al*, 1988). Our study population comprised 21 patients with OCD who manifested sustained improvement during 5 to 27 months of treatment with clomipramine and who were withdrawn from clomipramine in a two-dose staged process over a 4-day period. Of the 18 patients who completed the study, 16 experienced profound worsening of OC symptoms within 7 weeks of clomipramine discontinuation. Worsening became statistically significant 4 weeks after clomipramine discontinuation and appeared unrelated to treatment duration prior to discontinuation of clomipramine or to the OC symptoms at presentation. Reinstitution of clomipramine in an open fashion at the completion of the discontinuation phase led to symptom remission, with the patients returning to their pre-discontinuation levels of improvement. A possible inference of the study is that prolonged clomipramine administration is warranted for the majority of patients with OCD. However, further studies are needed to evaluate whether relapse can be more successfully avoided by using a more gradual discontinuation of clomipramine or by prolonging treatment beyond the period examined (a mean of 10.7 ± 5 months).

To investigate further the relationship between clomipramine's potent serotonergic effects and its clinical efficacy, we administered the 5-HT receptor antagonist, metergoline, to patients with OCD who had been receiving clomipramine on a long-term basis (Benkelfat *et al*, 1989). The patients showed improvement with clomipramine, manifesting an average 40% lessening of OC symptoms. In this placebo-controlled cross-over study, carried out under double-blind, random-assignment conditions, the OCD patients became progressively more anxious and obsessional during metergoline administration than during placebo administration, with differences becoming statistically significant by day 4 (Fig. 1). Metergoline's lowering of plasma prolactin concentrations provided evidence of its physiologically significant 5-HT antagonism. Plasma clomipramine concentrations remained unchanged during metergoline co-treatment, further supporting the hypothesis that clomipramine's therapeutic effects in OCD are mediated via serotonergic mechanisms.

More highly selective 5-HT uptake inhibitors that are effective antidepressant drugs have recently become available (Table I; Hyttel & Larsen, 1985; Heym & Koe, 1988; Frazer & Brunswick, 1989). Two studies evaluated fluvoxamine under fully controlled conditions in patients with OCD (Perse *et al*, 1987; Goodman *et al*, 1989). In both, fluvoxamine was found to be more effective than placebo. Not only are these 5-HT uptake inhibitors and their metabolites highly 5-HT selective, but they also have negligible anticholinergic activity (Hyttel & Larsen, 1985; Frazer & Brunswick, 1989). Their actions thus affirm some of the suppositions

TABLE III
Controlled comparisons of clomipramine (CMI) versus desipramine (DMI) in patients with obsessive–compulsive disorder

Result	*Dose (mg/day)*	*Design, n*	*Reference*
CMI > DMI	235, 290	Cross-over, 10	Zohar & Insel (1987)
CMI > DMI	3 mg/kg, as tolerated	Cross-over, 21	Leonard *et al* (1988)

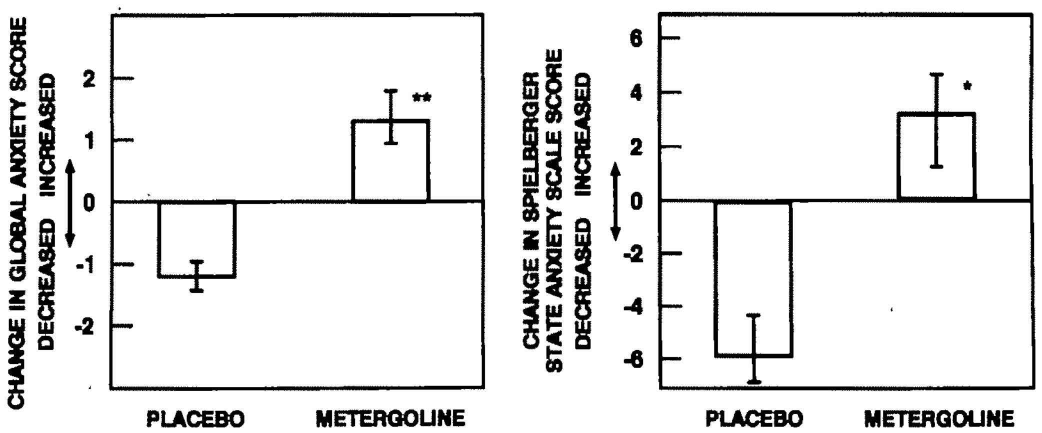

Fig. 1 Peak behavioural rating changes (mean ± s.e.m.) from baseline in response to 4 days administration of placebo or metergoline (4 mg/day) administered orally under double-blind, random-assignment conditions to patients with OCD treated on a long-term basis with clomipramine. $^{*}P<0.05$, $^{**}P<0.01$, paired *t*-test, placebo v. metergoline differences from baseline (adapted from Benkelfat *et al*, 1989).

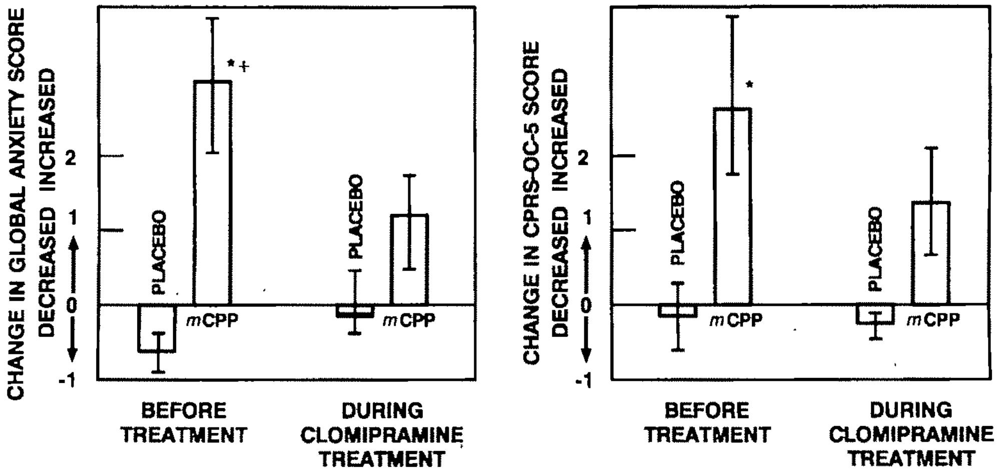

Fig. 2 Peak behavioural changes (mean ± s.e.m.) from baseline on behavioural ratings before and after 4 months of clomipramine treatment. Placebo and *m*-CPP were administered orally under double-blind random assignment conditions to patients with OCD. CPRS-OC-5 indicates Comprehensive Psychiatric Rating Scale-Obsessive-Compulsive 5-item subscale. $^{*}P<0.05$, paired *t*-test, placebo v. *m*-CPP-induced differences from baseline; $+P<0.05$, paired *t*-test, *m*-CPP-induced changes from baseline (pre-clomipramine treatment) v. during clomipramine treatment (adapted from Zohar *et al*, 1989).

regarding serotonergic contributions in the treatment of OCD that were derived from the earlier studies with clomipramine.

The functional status of serotonergic subsystems in OCD patients

All the treatment studies cited above concur with the hypothesis that the antiobsessional effects of pharmacological agents such as clomipramine, fluoxetine, and fluvoxamine may be associated with their potent serotonergic activity. However, whether patients have a psychobiologic abnormality involving serotonergic functioning is an entirely different question. Approaches to finding an answer are usually based on comparisons of various indirect indices of brain 5-HT in drug-free patients with OCD and matched controls. Thus, a few studies have examined 5-HIAA concentrations in cerebrospinal fluid, 5-HT concentrations in platelets,

[^{3}H]-imipramine binding in platelets, and, more recently, behavioural and endocrine responses to pharmacological challenges with selective serotonergic agonists.

The 5-HT metabolite, 5-HIAA, in the cerebrospinal fluid may serve as an indicator for central 5-HT turnover (for reviews, see Post & Murphy, 1979; Jimerson & Berrettini, 1985). Significantly difference (30% higher) 5-HIAA concentrations in cerebrospinal fluid were reported in a small group of patients ($n = 8$) with OCD when compared with 5-HIAA values corrected for height and weight of 23 controls (Insel *et al*, 1985). In a larger study, Thorén and co-workers (1980*a*) did not find significantly higher 5-HIAA concentrations in cerebrospinal fluid, although 5-HIAA levels were 20% higher in patients with OCD compared to controls. The higher levels of 5-HIAA in the cerebrospinal fluid of patients with OCD would be of interest because impulsive and violent patients, who are phenomenologically opposite to those with OCD, have 5-HIAA levels that are significantly lower than controls (Linnoila *et al*, 1983; van Praag, 1983; Virkkunen *et al*, 1987).

High-affinity [^{3}H]-imipramine binding sites in human platelets closely resemble imipramine binding sites in the human brain (Rehavi *et al*, 1984) and are closely associated with the pre-synaptic uptake site for [^{3}H]-5-HT (Paul *et al*, 1981). Thus, high-affinity [^{3}H]-imipramine binding may serve as a model of some relevance for central serotonergic neurons (Lingjærde, 1984). [^{3}H]-imipramine binding sites were found to be significantly different (50% lower) in 18 patients with OCD when compared with 18 age- and sex-matched controls in a recent study by Weizman *et al* (1986), although a similar difference was not found in a study conducted by Insel *et al* (1985).

To investigate further the possible role of 5-HT in mediation of obsessional symptoms, our group examined the behavioural, thermal, and neuroendocrine responses to direct activation of the serotonergic system with the selective 5-HT receptor against, *m*-chlorophenylpiperazine (*m*-CPP), in untreated patients with OCD and healthy controls (Zohar *et al*, 1987*a*). Traditional drugs that affect serotonergic metabolism and action such as L-tryptophan or L-hydroxytryptophan are not entirely specific for the serotonergic system (Fernstrom & Wurtman, 1974; Saavedra & Axelrod, 1974), or they are associated with severe adverse effects, as seen with *p*-chlorophenylalanine (Engelman *et al*, 1967). Some other direct post-synaptic receptor agonists, such as dimethyltryptamine (Meltzer *et al*, 1982), are not useful because of hallucinogenic properties. Our earlier studies with *m*-CPP demonstrated that it led to highly reproducible dose-dependent effects on prolactin, cortisol, and temperature in normal volunteers (Mueller *et al*, 1985*a*,*b*) and rhesus monkeys (Aloi *et al*, 1984). These neuroendocrine and thermal effects were blocked by the 5-HT$_1$/5-HT$_2$ antagonist, metergoline (Mueller *et al*, 1986). *m*-Chlorophenylpiperazine is a synthetic, non-indole, aryl-substituted piperazine that rapidly crosses the blood–brain barrier (Samanin *et al*, 1979; Fuller *et al*, 1980). It is a metabolite of the antidepressant, trazodone (Caccia *et al*, 1981), and thus might be expected to be safe and well tolerated in humans. *In vitro* studies with *m*-CPP showed potent displacement of tritiated 5-HT from membrane homogenates (Fuller *et al*, 1981; Invernizzi *et al*, 1981). *In vivo* administration of *m*-CPP in pre-clinical biochemical studies led to decreased central 5-HT synthesis and turnover (Samanin *et al*, 1980; Fuller *et al*, 1981), which was interpreted as a feedback effect following post-synaptic receptor stimulation. In animal studies, *m*-CPP produces typical changes in 5-HT-mediated behaviours such as decreased food consumption (Samanin *et al*, 1979; Mennini *et al*, 1980) and decreased locomotion (Vetulani *et al*, 1982); neuroendocrine responses such as increased prolactin, cortisol, and adrenal corticotropin levels (Maj & Lewandowska, 1980; Aloi *et al*, 1984); and physiologic responses such as hyperthermia (Aloi *et al*, 1984), which can be expected with some post-synaptic 5-HT receptor agonists. All these changes are reversed by administration of the 5-HT receptor antagonist, metergoline, and are responsive to presumed alterations in 5-HT receptor sensitivity produced by lesions and drugs (Samanin *et al*, 1979; Maj & Lewandowska, 1980; Aloi *et al*, 1984).

Using *m*-CPP as a probe of the functional status of the brain serotonergic system, we investigated whether patients with OCD would differ from healthy controls in their behavioural, neuroendocrine, or thermal responses to *m*-CPP and whether *m*-CPP would affect OCD symptoms. Responses to single oral doses (0.5 mg/kg) of *m*-CPP in the patients with OCD were compared with responses to placebo under double-blind, random-assignment conditions on separate days (Zohar *et al*, 1987*a*). Relative to healthy controls, the untreated patients with OCD became markedly more anxious (Fig. 2). They also described themselves as being more depressed and dysphoric. The response to placebo as well as the side-effects in both groups were mild and did not differ significantly between the patients and the controls (Zohar *et al*, 1987, 1988).

These results indicate that untreated patients with OCD are more responsive to the behavioural effects of *m*-CPP than healthy controls. However, the results did not indicate whether *m*-CPP would affect the symptoms of OCD. To evaluate this question, each patient in the study, with the help of a psychiatrist experienced in working with OCD patients, also completed specific ratings aimed at assessing changes in obsessions and compulsions.

Following administration of *m*-CPP, but not placebo, untreated patients with OCD experienced a transient but marked exacerbation of their OC symptoms (Fig. 1). The peak behavioural response was generally observed during the first 3 hours following *m*-CPP administration, and the duration of worsening ranged from several hours to 2 days. Moreover, following *m*-CPP, but not placebo, approximately half the patients spontaneously described emergence of new obsessions or re-occurrence of obsessions that had not been present for several months (Zohar *et al*, 1987*a*).

As oral administration of *m*-CPP has also been associated with anxiogenic effects in patients with panic disorder (Kahn *et al*, 1988*b*), it was not immediately clear whether *m*-CPP increased OC symptoms selectively or whether it caused non-specific exacerbation of diverse psychopathological responses. Certainly, *m*-CPP affected symptoms other than obsessions in the patients with OCD. The drug might, therefore, be considered primarily to increase anxiety or dysphoria and increase OC symptoms only as a secondary phenomenon. This possibility would be supported if patients with OCD were hypersensitive to other anxiogenic compounds. However, several recent studies with anxiogenic agents such as a lactate (Gorman *et al*, 1985), yohimbine (Rasmussen *et al*, 1987), and caffeine (Zohar *et al*, 1987*b*) failed to show an increase in either anxiety or OC symptoms in patients with OCD. It seems, therefore, that patients with OCD are not especially prone to respond to provocative agents that exacerbate symptoms in patients with non-OCD anxiety disorders. Also, OCD patients do not exhibit increased OC symptoms or anxiety in response to 5-HT precursors such as L-tryptophan (Charney *et al*, 1988) or to 5-HT-releasing agents such as fenfluramine (Insel *et al*, 1984; Hollander *et al*, 1988). Those agents, while sharing some neuroendocrine and other physiologic effects with *m*-CPP, also act at many other 5-HT subsystems that have been identified in animal brain studies. Some of these subsystems, such as the 5-HT_{1A} receptor, mediate responses that are opposite to those elicited by *m*-CPP in animals. For example, agents acting at 5-HT_{1A} sites in rodent brain elicit hypothermia, hypotension, increased food intake, and 'anxiolytic' responses in some animal models of anxiety. In contrast, *m*-CPP has hyperthermic, hypertensive, anorectic, and anxiogenic actions in rodents. Which 5-HT subtypes are responsible for the different effects of *m*-CPP remains controversial (see Murphy *et al*, 1989, for a review). Thus, *m*-CPP is the only agent so far that has been associated with exacerbation of OC symptoms in a placebo-controlled study (Zohar *et al*, 1987*a*).

In contrast to behavioural hypersensitivity, equivalent and statistically significant increases in prolactin and temperature were observed to follow *m*-CPP in both OCD patients and controls. In contrast, peak plasma cortisol concentrations after *m*-CPP were lower in the OCD patients than in controls; the OCD patients also tended to have lower baseline cortisol values than those of the controls. The lack of a differentially increased secretion of 'stress hormones' such as prolactin and cortisol (Mills, 1985) in OCD patients during an apparently stressful experience is a puzzling phenomenon. One possible interpretation of this response is that the effects of *m*-CPP on behaviour are mediated by a different mechanism than the effects of *m*-CPP on neuroendocrine and thermal regulation. The lack of difference in baseline prolactin or cortisol levels and temperature between patients and controls is consistent with that interpretation, which suggests in OCD patients only the 5-HT subsystem that mediates behavioural responses, including OC symptoms, is affected. In different brain areas 5-HT subsystems are known to modulate dopaminergic, cholinergic, and peptidergic systems (including the corticotropin-releasing hormone system), so it is not implausible that the behavioural effects of 5-HT might represent an interaction with one or another of these systems. Another possible interpretation is that the effects of *m*-CPP might bypass the normal stress control mechanisms that regulate the increased secretion of prolactin and cortisol. This interpretation was suggested by the reduced cortisol responses to *m*-CPP in patients with OCD compared with patients with panic disorder who exhibit increased cortisol responses to oral *m*-CPP (Kahn *et al*, 1988*a*).

A second study that examined the effects of *m*-CPP in OCD patients also found that these patients were behaviourally hyperresponsive to it (Hollander *et al*, 1988). A contrasting finding, which initially appeared discrepant with our results, was that *m*-CPP given intravenously to OCD patients and controls failed to elicit an increase in OC symptoms (Charney *et al*, 1988). In this study, both OCD patients and controls developed marked anxiety and many other psychological and somatic symptoms, results similar to observations from another study, which compared intravenous and oral *m*-CPP in healthy volunteers (Murphy *et al*, 1989). In a more recent study, we also found that IV *m*-CPP, administered either alone or following pre-treatment with metergoline, failed to elicit OC symptoms in OCD patients or controls (Pigott *et al*, unpublished). Investigator observations and patient self-reports indicated that the abrupt, severe provocation of anxiety and many somatic symptoms of short duration appeared to be such an overwhelming experience that most patients were distracted from any obsessional thoughts or compulsive rituals they had experienced prior to IV injection of *m*-CPP or during placebo administration (Pigott *et al*, unpublished). Thus, our present interpretation is that IV-administered *m*-CPP provides a response considerably different from that observed following orally administered *m*-CPP. In the latter procedure, OC symptoms developed progressively over several hours, a time period that closely parallels the duration of the neuroendocrine and thermal responses as well as the time course of plasma concentrations of *m*-CPP (Mueller *et al*, 1985*a*; Zohar *et al*, 1987*a*; Murphy *et al*, 1989).

Changes in the functional status of brain serotonergic subsystems in OCD patients during treatment with clomipramine

The observation that a 5-HT agonist like *m*-CPP is associated with acute exacerbation of OC symptoms — whereas agents such as clomipramine, fluvoxamine, and fluoxetine, which are believed to increase serotonergic function indirectly, decrease OC symptoms — raises many questions. Discrete effects of *m*-CPP on specific 5-HT subsystems have been well documented in rodent studies. They show the actions of *m*-CPP on food intake, body temperature, and locomotor activity to be opposite to those produced by selective $5HT_{1A}$ agonists such as 8-hydroxy-2(di-*n*-propylamino)tetraline (8-OH-DPAT) (Murphy *et al*, 1989). Another explanation for this apparent paradox, demonstrated in animal studies, is that long-term treatment with 5-HT uptake inhibitors leads to adaptive downregulation of 5-HT receptors (Fuxe *et al*, 1983; Ögren *et al*, 1985; Frazer *et al*, 1988).

To investigate possible changes in brain serotonin responsivity, *m*-CPP and placebo were given under double-blind conditions to nine patients with OCD before and after treatment with clomipramine (Zohar *et al*, 1988). Unlike our previous observations of a marked transient increase in obsessional symptoms and anxiety following *m*-CPP administration in patients not treated with clomipramine, readministration of *m*-CPP after 4 months of clomipramine treatment failed to increase obsessional symptoms and anxiety significantly (Fig. 2). Similarly, the hyperthermic effect of *m*-CPP that had been observed before treatment with clomipramine was eliminated after treatment. Interestingly, prolactin and cortisol responses to *m*-CPP appeared minimally altered by clomipramine treatment, although a comparison of *m*-CPP plasma levels before and during clomipramine treatment also raised the possibility of the development of subsensitivity in these responses (Zohar *et al*, 1988).

The ability of clomipramine to reduce OC symptoms in patients with OCD, coupled with the development of relative hyporesponsivity to *m*-CPP during clomipramine treatment, strongly suggests that the therapeutic effects of clomipramine in patients with OCD are associated with the development of subsensitivity in a 5-HT subsystem involved in OC symptoms and related behaviours. Still to be determined is whether a similar serotonergic subsystem downregulation occurs during the treatment of OCD patients with more highly 5-HT-selective uptake inhibitors such as fluoxetine, fluvoxamine, sertraline, and paroxetine and also during treatment with structurally different 5-HT agents such as buspirone and gepirone, which act at 5-HT_{1A} sites. Such studies to investigate responses to *m*-CPP in patients receiving fluoxetine are currently underway in our group. In addition, since we have preliminary evidence from a controlled study of buspirone that it has clinical efficacy in OCD patients (Pato *et al*, unpublished), investigations of buspirone's effects on responses to *m*-CPP have also been initiated.

Conclusions

Human behaviour is complex. Behavioural abnormalities such as obsessive–compulsive disorder are likely to be of heterogeneous origin, and numerous explorations of other psychobiologic aspects of OCD are underway (Baxter *et al*, 1987; Zohar & Insel, 1987; Karno *et al*, 1988; Rapoport, 1988; Nordahl *et al*, 1989). This paper has narrowly focused on the available evidence that links brain 5-HT function to obsessive–compulsive symptomatology. The largest body of relevant data is that based on studies showing OCD to be selectively responsive to drugs that inhibit synaptic 5-HT uptake and thereby modify brain serotonergic function. These agents are more effective in OCD than other neurotransmitter uptake inhibitors that are norepinephrine selective, such as desipramine or nortriptyline, or are non-selective. The fact that these agents and the 5-HT-selective agents have essentially equivalent therapeutic effects in depressed patients and in patients with panic disorder suggests that the 5-HT-selective drugs produce an antiobsessional effect somehow distinct, at least in OCD patients, from their antidepressant properties. Withdrawal of a 5-HT-selective agent in out-patients who have improved and substitution, under double-blind conditions, of either placebo (Pato *et al*, 1988) or desipramine (Leonard *et al*, 1988) is accompanied by a return of OCD symptoms. Brief co-administration of the 5-HT antagonist, metergoline, with clomipramine is also accompanied by a modest increase in OC symptoms in comparison to double-blind co-administration of placebo (Benkelfat *et al*, 1989). These data add further support to the proposition that 5-HT-related changes are an integral element in the therapeutic actions of 5-HT-selective drugs in OCD.

Therapeutic responses linked to serotonergic changes, however, do not necessarily implicate a primary serotonergic abnormality in patients with OCD. Few studies have been undertaken to measure 5-HT in blood platelets, 5-HIAA in cerebrospinal fluid, or other possible indirect indices of brain serotonergic function, such as radiolabelled imipramine binding in platelets. These few studies have produced little evidence to suggest a systematic, generalised abnormality in the synthesis, content, or metabolism of 5-HT in patients with OCD. More direct studies of brain 5-HT or 5-HIAA or of brain 5-HT receptors in OCD patients have not been accomplished.

Novel indirect approaches to the evaluation of brain 5-HT subsystems in OCD patients have, however, led to findings of pertinence. The fact that a selective serotonergic agonist, *m*-chlorophenylpiperazine, under specific experimental conditions can intensify current OCD symptoms or elicit dormant OC symptoms suggests a brain serotonergic subsystem abnormality in OCD. Although *m*-CPP is anxiogenic in psychiatric patients other than those diagnosed as obsessive–compulsive and, to a much lesser extent, in normals, the failure of non-serotonergic anxiogenic substances such as yohimbine or lactate to activate OCD symptoms (despite their leading to increased anxiety in non-OCD psychiatric patients) supports the attribution of OC symptom development to some 5-HT-mediated function. Finally, the significant attenuation of OC symptom worsening that is elicited by *m*-CPP in patients receiving clomipramine further validates an important role for an abnormal brain 5-HT subsystem in the disorder, one which can be ameliorated by 5-HT-selective drug treatment.

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Serotonergic Dysfunction in Depression

HERBERT MELTZER

Various irregularities in serotonin (5-HT) function have been postulated as causes of affective disorders. Serotonin has been related to many of the major symptoms of depression, e.g. mood, appetite, sleep, activity, and cognitive dysfunction. Interference with 5-HT synthesis or storage has been shown to induce depression in vulnerable individuals. Decreased levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid, decreased plasma tryptophan, low tryptophan neutral amino acid ratio, abnormalities in serotonergic function indicated by neuroendocrine challenge tests and various platelet measures, have been reported in depressed patients. Concentrations of 5-HIAA, the major metabolite of 5-HT in plasma, were found to be significantly negatively correlated with severity of depression as measured by the Hamilton Rating Scale for Depression score and specific depressive symptoms, despite the fact that plasma 5-HIAA is largely peripheral in origin. Blood platelets, which have been suggested as models for serotonergic nerve terminals, have a significantly decreased number of 5-HT uptake sites and ^{3}H-imipramine binding sites in depressed patients. Antidepressant drugs may act, in part, by enhancing serotonergic activity. The serotonergic deficit may occur at any of several levels: diminished availability of precursor, impaired activity of tryptophan hydroxylase, abnormalities in 5-HT release or uptake, 5-HT receptor abnormalities or interactions with other neurotransmitters.

Numerous neurotransmitters have been implicated in the biology of major depression, e.g. norepinephrine, acetylcholine, gamma-aminobutyric acid, dopamine, and serotonin (5-HT). There is evidence from biologic studies in depressed patients as well as inferential data from the mechanism of action of antidepressant drugs in laboratory animals and man to support some role for each of those neurotransmitters in the pathophysiology of depression. This paper will summarise briefly the evidence for the role of 5-HT in major depression. A more extensive discussion has appeared elsewhere (Meltzer & Lowy, 1987).

The 5-HT hypothesis of depression

The 5-HT hypothesis of affective disorders has been formulated in a variety of ways. One, proposed by Coppen (1967), Coppen *et al* (1972), and Lapin & Oxenkrug (1969) attributes increased vulnerability to either depression or mania, to decreased serotonergic activity. Deficiency of 5-HT has also been suggested as the proximate cause of depression (Koyama & Meltzer, 1986). On the other hand, Aprison *et al* (1977), among others, have postulated that increased serotonergic activity may cause depression. Most data favour the deficiency theory (Meltzer & Lowy, 1987; Coccaro *et al*, 1989).

Serotonergic abnormalities in depressed patients

Abnormalities in serotonergic function have been linked to many prominent symptoms of depression, e.g., appetite (Blundell, 1984), mood, sexual function, sleep dysfunction, and circadian rhythms (Meltzer & Lowy, 1987). A substantial body of evidence, in part to be reviewed here, reports serotonergic abnormalities in blood platelets, plasma, and cerebrospinal fluid (CSF) of depressed patients and post-mortem specimens from suicides, many of whom are presumed to have had a major depression or bipolar depression prior to suicide (Robins *et al*, 1959; Barraclough *et al*, 1974). Normal or decreased levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT in the cerebrospinal fluid of depressed patients or those who have made violent suicide attempts, further implicate diminished serotonergic activity in depression (Åsberg *et al*, 1984; Meltzer & Lowy 1987). A positive correlation between severity of depression and the cortisol response to 5-hydroxytryptophan (5-HTP) was observed (Meltzer *et al*, 1984*b*). This was attributed to an upregulation of 5-HT$_2$ receptors, possibly related to a deficiency in 5-HT.

Neuroendocrine challenge studies

Neuroendocrine challenge studies using serotonergic probes provide some measure of central serotonergic activity. We reported that the cortisol response to D,L-5-HTP, 200 mg was significantly greater in depressed patients than in normal controls (Meltzer *et al*, 1984*d*) (Fig. 1). Maes *et al* (1987) also found an enhanced cortisol response to L-5-HTP (200 mg, p.o.) in severely depressed females, compared with depressed males and in patients with minor depression (Fig. 2).

What is the effect of treatment with tricyclic

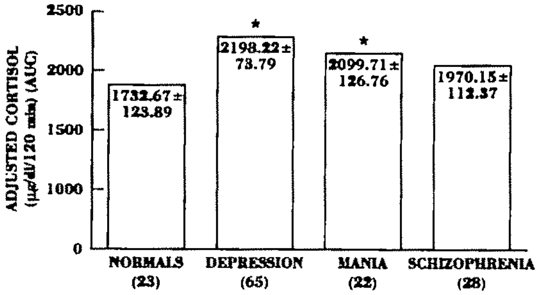

FIG. 1 5-HTP-induced increase in cortisol in normal controls and psychiatric patients.

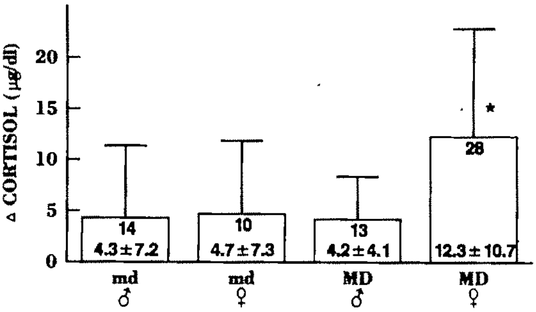

FIG. 2 Cortisol response after 5-HTP in controls and depressed patients (after Maes *et al*, 1987). md = minor depression; MD = major depression.

antidepressant drugs such as imipramine on 5-HTP-induced increases in cortisol? In our initial studies, which used half the dosage of 5-HTP in our currently used protocol, the tendency was toward a lesser — rather than greater — 5-HTP-induced increase in cortisol during treatment (Meltzer *et al*, 1984*b*). We have replicated that finding using L-5-HTP in a new series of depressed patients (Meltzer *et al*, unpublished data). Although it appears that blockade of 5-HT reuptake was achieved during treatment with the antidepressants, perhaps along with some alteration in 5-HT receptor sensitivity, no real enhancement of the response to 5-HT produced from the 5-HTP was seen. These results indicate that inhibition of uptake of 5-HT by such compounds may not be as marked as had been believed. On the other hand, there is stimulation of the 5-HTP-induced increase in serum cortisol with specific 5-HT uptake blockers such as sertraline and fluoxetine (Meltzer *et al*, unpublished). A significant negative relationship has been demonstrated between CSF 5-HIAA and the cortisol response to 5-HTP in major depression (Table I) that is consistent with the notion that decreased serotonergic activity is a factor responsible for enhanced response to 5-HTP in some depressed patients (Koyama *et al*, 1987). We suggested that this might be due to increased 5-HT_2 receptor sensitivity (Meltzer *et al*, 1984*b*), but this hypopthesis is not consistent with the normal cortisol responses observed following MK-212.

Plasma tryptophan

Some evidence has been presented that depressed patients may have lower plasma levels of tryptophan (Coppen & Wood, 1978; DeMyer *et al*, 1981) and, by implication, a decrease in 5-HT synthesis, because tryptophan concentration is believed to control the activity of tryptophan hydroxylase, the rate limiting enzyme in 5-HT synthesis. Cowen *et al* (1989) recently reported decreased plasma total tryptophan levels (primarily in female patients) in a small group of patients with depression. One study, however, showed no difference in plasma tryptophan levels in depressed patients (Møller, 1985). In our study, high-pressure liquid chromatography was employed to measure plasma tryptophan and 5-HIAA levels. No difference was found between the plasma tryptophan or 5-HIAA levels of 40 unmedicated patients diagnosed as having major

TABLE I
Spinal fluid metabolite correlations with 5-HTP-induced increase in serum cortisol

Metabolite	*n*	*CSF levels (ng/ml)* *Mean*	*s.d.*	*Correlation with 5-HTP-induced serum cortisol response (rho)*
5-HIAA	16	12.2	10.2	−0.65*
HVA	16	34.6	13.5	−0.46
DOPAC	16	2.7	2.1	0.21
MHPG	16	7.2	2.4	0.43

*$P = 0.05$.

Abbreviations: *n*, number of patients; s.d., standard deviation; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; DOPAC, 3,4-dihydroxyphenylacetic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

TABLE II
Plasma tryptophan and 5-HIAA in unmedicated depressed patients and normal controls

Group	*n*	*Tryptophan* (*μg/ml*)	*5-HIAA* (*ng/ml*)
Normal controls	17	8.69±2.26	5.52±1.67
Depressed patients	40	8.07±1.88	5.58±2.02

No significant differences noted.

depression and 17 normal controls (Table II). However, significantly lower fasting plasma tryptophan levels were found in both depressed female patients and female control subjects, a possible contributory factor to why females are more vulnerable to depression.

Møller *et al* (1980) have pointed out that a relative elevation of the concentration of large neutral amino acids may also contribute to a deficiency of brain 5-HT in depression, because plasma tryptophan must compete with those amino acids for entry into the brain. Determination of plasma free tryptophan and the concentration of neutral amino acids may be more revealing than the measure of tryptophan reported. Cowen *et al* (1989) also found a significantly lower ratio of plasma tryptophan to neutral amino acids in depressed patients.

Koyama & Meltzer (1986) attempted to replicate the findings of Charney *et al* (1984) and those of Heninger *et al* (1984), who reported a blunted plasma prolactin response to an intravenous tryptophan load (100 mg/kg over 20 min) in unmedicated depressed patients. We also measured the increase in plasma tryptophan levels and found them lower in depressed patients. Although the findings of a low prolactin response were replicated, when the difference in plasma tryptophan levels was co-varied, no blunting of the prolactin response was found. However, the study did show a striking inhibition of the growth hormone response that persisted even after adjustment for differences in tryptophan levels. This finding further suggests inadequate 5-HT production in depressed patients or perhaps diminished responsiveness of the 5-HT receptor subtype that mediates the growth hormone response.

In the study that showed markedly smaller increases in plasma tryptophan in depressed patients, plasma 5-HTP and 5-HIAA levels were also measured following the tryptophan infusion (Koyama & Meltzer, 1986). A non-significant trend toward lower 5-HTP levels was observed, whereas a markedly decreased level of 5-HIAA was found. Those results are consistent with the possibility that tryptophan might be metabolised via other pathways or perhaps be incorporated into proteins. Either way, these results suggest inadequate conversion of tryptophan to 5-HT in some depressed patients.

TABLE III
Univariate correlations between plasma 5-HIAA and psychopathology in major depression

Variable	*n*	*Spearman rho*	*P*
Hamilton-DEP (Total)	25	−0.42	0.04
Guilt	25	−0.46	0.02
Suicide	25	−0.38	0.06
Insomnia, late	25	−0.51	0.009
Hopelessness	25	−0.53	0.007
Worthlessness	25	−0.46	0.02

Plasma 5-hydroxyindoleacetic acid

Plasma 5-HIAA levels in unmedicated depressed patients were significantly negatively correlated with severity of depression as measured by the total Hamilton Rating Scale for Depression (Hamilton, 1960) and with the following items: guilt, suicide, insomnia, hopelessness, and worthlessness (Table III). These results suggest that plasma 5-HIAA concentration could be an indicator of brain serotonergic activity. This rather surprising finding needs to be replicated in an independent sample because numerous peripheral factors, such as metabolism of 5-HT in the gut affect plasma 5-HIAA levels.

The blood platelet as a model for brain 5-HT neurons

The blood platelet has been often suggested as a model for serotonergic nerve terminals, and it has, therefore, been used to study various aspects of 5-HT chemistry in man as well as the effect of antidepressant drugs on the 5-HT system. Coppen *et al* (1978), Meltzer *et al* (1981), and Healy *et al* (1986) found a decreased number of 5-HT uptake sites in the platelets of depressed patients. Our research has shown this decrease to be most marked in bipolar and psychotically depressed patients (Table IV). A marked decrease in platelet ^{3}H-impramine binding sites was also found in these patients (Meltzer *et al*, 1984*a*).

We have studied children, aged 6 to 18 years, who were suffering from major depressive disorder or were in recovery from major depressive disorder for less than 2 months (Ambrosini *et al*, unpublished). The control group consisted of normal subjects and non-depressed psychiatric patients. Significantly decreased numbers of ^{3}H-imipramine binding sites (B_{max}) were found in the depressed children. No difference in the number of platelet 5-HT uptake sites was detected, however. In a separate group of recovered depressed children, we

TABLE IV

Platelet 5-HT uptake in psychiatric disorders

Group	*n*	K_m *(µm)*	V_{max} *(pmol/10^7 platelets per min)*
Normal controls	140	0.47±0.13	12.5±2.9
Major depression	100	0.43±0.13	9.7±2.9*
unipolar	63	0.43±0.13	10.4±2.9*
bipolar	37	0.43±0.12	8.5±2.9*
psychotic	52	0.43±0.13	9.1±3.2*
non-psychotic	48	0.44±0.12	10.4±2.6*
Unipolar psychotic	23	0.43±0.12	10.1±2.9
Unipolar non-psychotic	40	0.44±0.13	10.6±2.8
Bipolar psychotic	29	0.43±0.13	8.4±2.9*
Bipolar non-psychotic	8	0.44±0.13	9.0±3.0*
Schizoaffective depressed			
mainly affective	10	0.44±0.14	8.4±2.8*
mainly schizophrenic	13	0.48±0.15	11.1±5.4
Manic	38	0.45±0.13	9.8±2.1*
Schizophrenic	84	0.45±0.13	10.9±3.3

*Significantly less than normal controls.

found that the number of ^{3}H-imipramine binding sites was also within normal limits.

Suranyi-Cadotte *et al* (1985) and others have reported decreased ^{3}H-imipramine binding in the frontal cortex of suicides. We have been unable to replicate the finding of decreased ^{3}H-imipramine binding in the frontal cortex of suicide victims (Arora & Meltzer, in press). Gross-Isseroff *et al* (1989) also found no difference in ^{3}H-imipramine binding in the pre-frontal cortex of suicide victims, but did find increases in the hippocampus and decreases in the post-central cortical gyrus, insular cortex, and claustrum. These results as well as those of others (Demeter *et al*, 1986) imply that abnormalities in the serotonergic system of depressives and suicides may be region-specific.

A 5-HT$_2$-like receptor in platelets has been described that has features comparable to those of brain 5-HT$_2$ receptors (Geany *et al*, 1984). Two studies have now found that depressed patients have higher numbers of 5-HT$_2$ receptors in platelets. Biegon *et al* (1987) reported increased numbers of 5-HT$_2$ sites in blood platelets of unmedicated depressed patients. We have also found an increase in the number of 5-HT$_2$ binding sites using ^{3}H-lysergic acid diethylamide as a ligand (Arora & Meltzer, 1989*b*). Biegon *et al* (1987) using ketanserin reported that the number of sites was normalised after 4 weeks of antidepressant therapy. These studies are of interest in light of the reports of increased numbers of 5-HT$_2$ binding sites in the frontal cortex of suicides (Mann *et al*, 1986; Arora & Meltzer, 1989*a*).

Serotonergic basis of effective treatment of depression

A considerable body of evidence from both pre-clinical and clinical studies shows that chronic administration of the following can enhance serotonergic activity: tricyclic antidepressants, specific 5-HT uptake inhibitors, MAO inhibitors, precursors of 5-HT, electroconvulsive therapy, and lithium (Meltzer & Lowy, 1987). These modalities may act as antidepressants by correcting or compensating for an underlying deficit in the serotonergic system.

We are studying the effects that specific serotonergic blockers, such as fluoxetine, have on the 5-HTP-induced increase in serum cortisol in unmedicated depressed or obsessive–compulsive patients. Treatment with the 5-HT uptake blockers produce an enhancement in the cortisol response not evident with non-specific tricyclic agents, such as desipramine, nortriptyline, and amitriptyline (Meltzer *et al*, unpublished). This enhancement may reflect the specific 5-HT uptake inhibitor's ability to more effectively block 5-HT uptake in the brain, although the tricyclics are effective inhibitors of 5-HT uptake in platelets. However, the effect of the direct acting 5-HT agonist, MK-212 on cortisol secretion is also enhanced by 4 to 6 weeks of treatment with fluoxetine, but not by commonly used tricyclic antidepressants (Meltzer *et al*, unpublished). These results suggest that if the MK-212 response is indeed a 5-HT-mediated effect, then an upregulation of 5-HT receptors with the specific 5-HT uptake blockers

TABLE V
Multivariate prediction of SADS-C Depression Scale score from CSF metabolites in major depression

Variable	*Standard estimate*	*P*
HVA	−0.55	0.06
5-HIAA	0.44	0.13

$F = 1.981$; d.f. = 2, 22; $P = 0.16$.

(e.g. fluoxetine) can be achieved that is not evident with common tricyclic agents. Such an effect may well be 5-HT receptor selective. If a serotonergic deficiency is present in depression, upregulation of 5-HT_2 receptors might occur to compensate for diminished serotonergic activity. These findings may explain why drugs such as fluoxetine are more effective in treating obsessive–compulsive disorder. One would expect them also to be more effective as antidepressants if enhancement of serotonergic activity is so critical for the treatment of depression but this does not appear to be the case. This apparent inconsistency with the 5-HT hypothesis of depression must be explained, or current hypotheses of the role of 5-HT as a specific cause of depression will have to be modified.

Induction of depression

The induction of depressed mood or depression by decreasing 5-HT synthesis presents more compelling evidence for the relationship between 5-HT and depression. Interfering with 5-HT synthesis or storage by administering parachlorphenylalanine (PCPA) (Shopsin *et al*, 1976) or reserpine (Goodwin and Bunney, 1971) has induced depression in vulnerable individuals. Recent studies suggest that a reduction of dietary tryptophan, coupled with an increase in neutral amino acids, can bring about depressive symptoms even in normal subjects (Young *et al*, 1986; Smith *et al*, 1987). Similar results have now been reported in major depressives (Heninger *et al*, 1989). These findings strongly suggest the need for a tonic serotonergic effect to maintain normal mood.

Relationship to other neurotransmitters

Our group has measured CSF 5-HIAA and homovanillic acid (HVA), the major metabolite of dopamine, in 30 patients with major depression and 18 schizophrenic patients who had undergone at least a one-week washout period. The CSF data were log-transformed for normalisation. There were significantly lower CSF 5-HIAA levels in the depressed patients (105.2±33.2 nmol/litre v. 128.2±35.0 nmol/litre (P=0.03); CSF HVA levels were also significantly lower in the depressed patients (167.6±65.0 nmol/litre versus 213.8±82.7 nmol/litre) than in the schizophrenic patients. The concentrations of CSF HVA were not significantly correlated with the Depression Subscale of the Schedule for Affective Disorders and Schizophrenia (SADS-C; Endicott & Spitzer, 1978). There was also no relationship between suicide ratings and CSF 5-HIAA or HVA levels. We found a highly significant correlation between CSF 5-HIAA and HVA in depressed patients (rho = 0.62, n = 30, P = 0.0001). A recent summary by Potter *et al* (1987) of the studies of CSF levels of 5-HIAA and HVA in depression concluded that the most consistent finding was a decrease in HVA, not a decrease in 5-HIAA concentrations.

Because of the high correlation between CSF HIAA and HVA levels, a multivariate analysis to predict severity of depression from both variables was carried out. There was a nearly significant negative relationship between CSF HVA and SADS-C depression ratings after adjusting for 5-HIAA levels (Table V). This suggests low dopaminergic activity may be a predictor of severity of depression.

Causes of 5-HT deficit

Several causes for the postulated 5-HT deficit in depression have been discussed. Diminished availability of 5-HT may be caused by limited precursor, by changes in activity of tryptophan hydroxylase, or by abnormalities in release or reuptake of 5-HT at the synapse. A functional deficit of 5-HT relative to other neurotransmitters of neuromodulators may occur. 5-HT receptors may show abnormalities, with a subsensitivity of one or more subtypes, or an abnormal interaction may occur between 5-HT receptor subtypes.

Second messenger systems linked to 5-HT receptors may be abnormal in depression. Further inquiry is necessary into the possibility that function of either adenylate cyclase, which is the second messenger for the 5-HT_2 receptor, may be anomalous.

We found no evidence in our studies that 5-HT receptor subsensitivity was a primary causal factor in depression. Our examination of 5-HT binding in those who had committed suicide revealed an upregulation of both the 5-HT_1 and 5-HT_2 sites in some subtypes rather than a decrease (Matsubara & Meltzer, unpublished; Arora & Meltzer, 1989*a*,*b*).

Various behaviours influenced by 5-HT may depend on an interaction between 5-HT receptor subtypes (Pericic & Manev, 1988). The possibility exists that such an interaction between two subtypes (both of which might be upregulated) leads to a net decrease in 5-HT-regulated behaviour.

Summary

A variety of evidence implicates 5-HT in depression. Current genetic data indicate that heterogeneity is present in bipolar depression, suggesting the probable involvement of various neurotransmitters. Similar abnormalities need not necessarily occur in all patients with major depression. Therefore, variance between subjects could make detection of specific abnormalities difficult. The evidence reviewed here suggests that diminished availability of 5-HT is one of the crucial factors in depression. Low plasma tryptophan levels, a low tryptophan-neutral amino acid ratio, and the difference in achieved levels of tryptophan following a tryptophan load are consistent with this. Decreased ^{3}H-imipramine binding and decreased uptake changes in platelet are difficult to interpret. Future studies must investigate the issue of inactivation of 5-HT in depression at the CNS level.

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The Antidepressant Effects of 5-HT Uptake Inhibitors

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The functional roles of monaminergic transmitters in depression have been widely studied during the past decade. Data from that research suggest that lower levels of the 5-HT metabolite, 5-HIAA, in the cerebrospinal fluid; 5-HT uptake in human platelets; and platelets [^{3}H]-imipramine binding sites occur in depressed patients. In recent years several potent and selective 5-HT uptake inhibitors have become available for clinical studies. The first shown to have antidepressant effects, zimelidine, was followed by similar compounds such as femoxetine, fluvoxamine, citalopram, indalpine, fluoxetine, paroxetine, and sertraline. The effectiveness of serotonin inhibitors in treating other disorders, such as obsessive–compulsive disorder, anxiety, and panic disorder, has also been demonstrated. This review reports the data from clinical studies with these agents. The 5-HT uptake inhibitors are devoid of anticholinergic properties and have not produced weight gain or sedative side-effects, but may have another profile of side-effects. Headache, nausea, and vomiting have been reported, however.

Research evidence during the last few decades indicates a possible relationship between disturbances in central neuroaminergic neurotransmission and affective disorders (Glowinski & Axelrod, 1964; Shildkraut, 1965; Coppen, 1967; Lapin & Oxenkrug, 1969; Åsberg *et al*, 1976). The relative importance of 5-hydroxytryptamine (5-HT, or serotonin) and norepinephrine (NE) has been proposed and even formulated into the hypothesis that certain depressions are related to a functional deficit of 5-HT while others are the result of a functional deficit of NE. Biochemical support of 5-HT hypotheses comes from findings that include lower 5-hydroxyindoleacetic acid (5-HIAA) levels in the cerebrospinal fluid of depressed patients compared with healthy controls (Åsberg *et al*, 1976); low concentrations of 5-HT or 5-HIAA in the brain of suicide victims at autopsy (Shaw *et al*, 1967; Korpi *et al*, 1986) lower 5-HT uptake by platelets (Tuomisto & Tukiainen, 1976; Coppen *et al*, 1978). Therefore development of selective inhibitors of pre-synaptic neutral transmitter uptake by the neurons is of theoretical as well as therapeutic interest. In recent years, several potent, selective 5-HT uptake inhibitors have become available for clinical study, and this paper will review the results of that research.

Antidepressant efficacy of 5-HT uptake inhibitors

Short-term treatment

The most practicable means of deciding whether a drug possesses antidepressant efficacy is to use placebo control. Active comparison trials without placebo control almost always suffer from Type II errors due to insufficient sample size. Table I displays the results of well designed placebo-controlled antidepressant trials of the following 5-HT uptake inhibitors: zimelidine, fluoxetine, fluvoxamine, sertraline, citalopram and trazodone.

There are no data available from placebo-controlled studies for the other 5-HT uptake inhibitors paroxetine, femoxetine or indalpine. Trazodone, although possessing 5-HT uptake inhibiting properties, also possesses other biochemical properties and thus may not be considered a specific 5-HT uptake inhibitor (Riblet *et al*, 1979).

In general, compounds of this class have demonstrated clinically relevant efficacy. The outcomes of these studies are summarised in Table I. In Table II, a tabulation of the positive and non-significant place-controlled studies shows that all compounds have demonstrated efficacy in at least one study. Comparative studies with other antidepressants can provide information on side-effects and rate of response. These studies are displayed in Table III. Not unexpectedly, the majority of studies failed to differentiate the compounds on items of efficacy.

In general, the 2- to 3-week delay in onset of action is comparable to other standard antidepressants. Several studies have described an earlier response with 5-HT uptake inhibitors such as zimelidine (Wålinder *et al*, 1981), fluvoxamine (Feldmann & Denber, 1982), and fluoxetine (Holsboer *et al*, 1986). However, these findings have not yet been satisfactorily replicated.

Long-term treatment and prophylaxis

Another aspect of the management of depression is long-term treatment to prevent relapses or new episodes. From a theoretical point of view, it is worth noting that 5-hydroxytryptophan was found to be effective in prophylactic treatment of depression. This efficacy was most pronounced in patients with low 5-HIAA in the cerebrospinal fluid (van Praag, 1981).

TABLE I

Placebo-controlled studies with selective 5-HT uptake inhibitors

		No. of patients	*Treatment period (weeks)*	*Outcome*
Zimelidine (Z)	Norman *et al* (1983)	Z = 14 P = 14	6	Z > P
	Merideth & Feighner (1983)	Z = 39 I = 38 P = 42	6	Z > P = 1
	Claghorn *et al* (1983)	Z = 127	4	Z = A > P
Fluoxetine (FX)	Cohn & Wilcox (1985)	FX = 54 I = 54 P = 58	6	FX = I > P
	Stark & Hardison (1985)	FX = 185 I = 186 P = 169	6	FX = I > P
	Reimherr *et al* (1984)	FX = 68 I = 44 P = 30	6	FX = I > P
	Fieve *et al* (1986)	FX = 35 P = 35	6	FX > P
	Fabre & Crismon (1985)	FX = 22 P = 26	5	FX > P
Fluvoxamine (FV)	Itil *et al* (1983)[1]	FV = 22 I = 25 P = 22	3	FV < I > P
	Norton *et al* (1984)[1]	FV = 33 I = 30 P = 25	4	FV = I = P
	Dominguez *et al* (1985)	FV = 35 I = 35 P = 31	4	FV > P = I
	Amin *et al* (1984)	FV = 169 I = 161 P = 151	4	FV = I > P
Sertraline (S)	Reimherr *et al* (1988)	S = 26 A = 26 P = 25	8	S = A > P
	Fabre *et al* (Preliminary info.)	S = 278 P = 91	6	S > P
Citalopram (C)	Fabre *et al* (Preliminary info.)	C = 83 P = 87	4	C > P
	Herrington & Worrel (Preliminary info.)	C = 28 P = 28	6	C = P
Trazodone (T)	Feighner (1980)	T = 17 I = 18 P = 10	4	T = I >P

Continued

TABLE I (continued)

		No. of patients	*Treatment period (weeks)*	*Outcome*
	Kellams (1979)	T = 13 I = 12 P = 11	4	T = I > P
	Escobar (1980)	T = 13 I = 15 P = 12	4	I > T = P
	Mann (1980)	T = 10 I = 9 P = 9	4	T > P = I

P Placebo.
1. Centres contributing to Amin *et al* (1984).
> indicates superiority at 5% level of significance.
= fails to show superiority at the 5% level of significance.

TABLE II
Overview of placebo-controlled studies

Compound	*No. of placebo studies*	*No. showing superiority*	*No. failing to show superiority*
Zimelidine	3	3	—
Fluoxetine	5	5	—
Fluvoxamine	4	2	2
Sertraline	2	2	—
Citalopram	2	1	1
Trazodone	4	3	1

In a placebo-controlled study conducted by Björk (1983), zimelidine was found to be significantly more effective than the placebo, and in terms of preventing recurrence and in minimising the withdrawal rate over a period of 18 months. Fluoxetine was found to be as effective as imipramine in open-label extensions of double-blind clinical trials of from 1–5 years (Wernicke & Bremner, 1986). Fourteen patients treated with citalopram for 8–113 weeks showed favourable results (Pedersen *et al*, 1982).

In our unit at Danderyd hospital, 10 patients who had not responded to other drugs or to lithium have now been treated with zimelidine for 5–8 years. The effect of zimelidine has been superior compared with earlier treatment, both in preventing relapse and/or in avoiding side-effects.

Sertraline, one of the new as yet unmarketed 5-HT inhibitors, demonstrated efficacy in preventing relapse and recurrence of depression (Doogan & Caillard, 1988). In Figure 1, the rate of relapse is displayed using Kaplan–Meier survival estimates. It is apparent that, in this placebo-controlled study, sertraline shows early significant differences from placebo that are maintained throughout the long-term (44-week) study (D. P. Doogan, personal communication).

Another important consideration in treatment is the effect of pharmacotherapy in elderly patients. The pharmacodynamic profile of the 5-HT uptake inhibitors which have no effect on muscarinic and adrenergic receptors, increases the possibility for success in treating the older population.

Much work remains to be done. Selective 5-HT uptake inhibitors are still new drugs, and for most of them, the therapeutic dose range has not yet been defined. Similar therapeutic effects have been reported with different dosages. In a study using citalopram (Bjerkenstedt *et al*, 1985) and another with fluoxetine (Wernicke *et al*, 1988), no significant differences in outcome between treatment groups were found with different doses. Until now, no one study has

TABLE III
Double-blind active control studies
5-HT uptake inhibitors versus tricyclic antidepressants

		No. of patients	*Outcome*
Zimelidine (Z)	Huitfeldt & Montgomery (1983)	97	Z = Amitriptyline
	Hiramatsu *et al* (1983)	95	Z = Imipramine
	Åberg-Wistedt *et al* (1982*b*)	65	Z = Desipramine
	Nyström & Hällström (1985)	75	Z = Mianserin
Fluoxetine (FX)	Bremner (1984)	40	FX > Imipramine
	Chouinard (1985)	51	FX = Amitriptyline
	Levine *et al* (1987)	60	FX = Imipramine
	Young *et al* (1987)	50	FX = Amitriptyline
Fluvoxamine (FV)	Klok *et al* (1981)	36	FV = Clomipramine
	Dick & Ferrero (1983)	32	FV = Clomipramine
	de Wilde *et al* (1983)	73	FV = Clomipramine
	Cuelfi *et al* (1983)	151	FV = Imipramine
	Guy *et al* (1984)	36	FV = Imipramine
Citalopram (C)	Gram *et al* (1986)	150	C > Clomipramine
	Gravem *et al* (1987)	43	C = Amitriptyline
Paroxetine (PX)	Laursen *et al* (1985)	44	PX = Amitriptyline
Femoxetine (FM)	Tamminen *et al* (1982)	45	FM = Amitriptyline
	Ahlberg *et al* (1982)	42	FM = Amitriptyline
	Skrumsager & Jeppesen (1986)	75	FM = Amitriptyline
Indalpine (IN)	Naylor & Martin (1985)	65	IN = Mianserine

= fails to show a significant difference.
> superior at 5% level of significance.

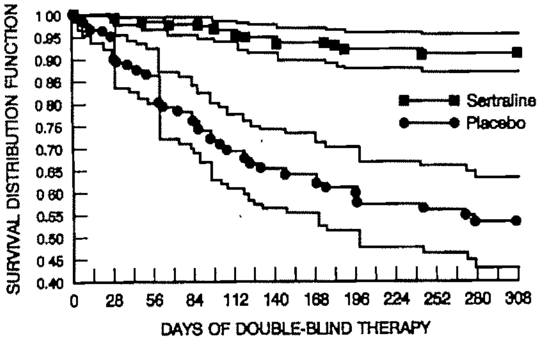

FIG. 1 Survival estimates and 95% confidence intervals by treatment group

demonstrated a correlation between clinical effect and plasma concentration. However, in a study with zimelidine, lower plasma levels of the metabolite, norzimelidine, were associated with a better response (Montgomery *et al*, 1982), whereas others found higher plasma levels of norzimelidine to be associated with poorer response (Wålinder *et al*, 1981; Wood *et al*, 1982).

Treatment specificity

Parallel group and open studies

In our research group, we have compared zimelidine with desipramine, a noradrenaline uptake inhibitor. We related clinical results to biochemical markers and found zimelidine responders had significantly lower levels of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid in the cerebrospinal fluid. The patients responded rapidly, showing relief of symptoms during the first week of treatment (Åberg-Wistedt *et al*, 1982*a*). However, it should be pointed out that the number of patients participating, (19) was small.

Lingjærde *et al* (1983) found a significantly positive correlation between improvement during zimelidine treatment and uptake inhibition in platelets. In a study comparing zimelidine to another noradrenaline uptake inhibitor, maprotiline, zimelidine was found to be significantly more effective in female patients with low 5-HT uptake in platelets (Nyström *et al*, 1986). Nyström & Hällström (1985) also found zimelidine to be superior to maprotiline in patients whose illnesses run a more chronic course.

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Those whose symptoms had not been relieved by other therapies have been found to respond well to zimelidine, as was demonstrated in the first clinical study of the drug by Siwers *et al* (1977). Similar observations were reported by Hiramatsu *et al* (1983) in a study comparing zimelidine with imipramine and placebo: zimelidine was superior for patients who had several previous episodes of depression, late onset of illness, and no favourable response to previous therapies. Reimherr *et al* (1984) found fluoxetine to be significantly more effective than imipramine in patients with a history of chronic depression and poor response to previous therapies. It is of particular interest that those two characteristics were also found in connection with a low level of 5-HIAA in the cerebrospinal fluid (Cronholm *et al*, 1977).

The effect of 5-HT uptake inhibitors on retardation does not seem to differ from that of standard tricyclics in most of the clinical studies. At this stage, therefore, it is difficult to delineate differences in effect on particular symptoms.

Cross-over studies

Cross-over studies contribute to an understanding of specificity, but the interpretation of their results is complicated. With protocols that specify a washout period of only 1 week, such studies may be flawed by carry-over effects from the first drug treatment period to the second. Two cross-over studies, by Åberg-Wistedt (1982*b*) and Lingjærde *et al* (1983), compared zimelidine with selective noradrenaline uptake inhibitors. Patients who were regarded as non-responders after 4 weeks of treatment were switched over to the other drug following 1 week of placebo. In both studies, when non-responders were switched, the second treatment was found to be significantly more effective. In the Åberg-Wistedt study, eight of 11 non-responders to desipramine ($n=32$) responded well to zimelidine ($n=32$), whereas three of four non-responders to zimelidine responded well to desipramine. Similar results were obtained in a zimelidine—desipramine cross-over study reported by Lingjærde in 1983. When Nyström & Hällström (1987) performed a cross-over study using zimelidine ($n=40$) and maprotiline ($n=35$), six of seven patients in each cross-over group responded to the second treatment.

It should be noted that in a cross-over study by Emrich *et al* (1987) using fluvoxamine ($n=12$) and oxaprotiline ($n=12$), only about 20% of the non-responders to one drug responded to the alternative. There, the treatment period with the first drug was 3 weeks, and non-responders were treated with the second drug after 1 week of placebo.

The results of those studies tend to support the existence of biochemical subgroups, but objections can be made to such an assertion. The number of patients studied was small and the relevance of the methodology may be questioned. It is noteworthy that the results of most studies indicate the newer drugs have the same response rates as reference drugs, so they affect depressed patients in whom 5-HT deficit is not a major biochemical deviation. Reimherr *et al* (1984) found no significant difference in the response to fluoxetine or imipramine in patients who had a history of good treatment response. It appears any selectivity of action was overwhelmed by the general antidepressant effect.

These findings do not point clearly to a specific subgroup of patients responding to the class of compounds.

Side-effects

The side-effects of the selective 5-HT uptake inhibitors are very similar. The most frequently reported side-effects are: gastrointestinal symptoms, such as nausea and vomiting; insomnia; nervousness and anxiety; and headaches.

Side-effects seem to be only moderately dose related. A study by Cooper (1988) of patients treated with fluoxetine found anxiety was reported in 15% of those receiving a 20-mg dose, 16% in patients receiving 40 mg, and 21% in those receiving 60 mg, compared with 11% in the placebo group. Nervousness was reported in 10% of patients receiving 20 mg, 15% in patients receiving 40 mg, and 19% in those receiving 60 mg, compared with 13% in the placebo group.

Insomnia can be related to reduced REM sleep as well as to reduced total sleep time and increased wakefulness, which were found with patients taking zimelidine and indalpine (Nicholson & Pascoe, 1986). Lack of sleep-inducing properties may influence the results of rating scores, especially on the Hamilton Rating Scale (Kragh-Sørensen, 1985; Chouinard, 1985).

The 5-HT uptake inhibitors differ from tricyclic antidepressants in anticholinergic side-effects, sedation, weight gain, and effects on blood pressure. The differences can be explained by an absence of effect on muscarinic, histaminic, and adrenergic receptors. Heym & Koe (1988) discussed the pharmacological evidence for the limited side-effect potential of sertraline. It has been found to lack a number of biological actions that are thought to lead to undesirable side-effects. Sertraline is not a strong sympathomimetic agent, nor does it possess significant anticholinergic activity. Due to its selectivity, it does not interact with histamine receptors, making significant sedation unlikely. Doogan & Caillard (1988) detail studies showing that sertraline has no meaningful binding affinity with muscarinic, dopamine, or alpha$_1$, alpha$_2$, or beta-adrenergic receptors.

The serious adverse reactions, influenza-like drug reaction and Guillain-Barré syndrome, which prompted the withdrawal of zimelidine from the market, have not been found during treatment with other 5-HT uptake inhibitors. Chouinard & Jones (1984) reported on one patient who failed to develop a serious reaction to fluoxetine after manifesting reactions with zimelidine.

Effects on anxiety and other disorders

Another question of interest is the effect of 5-HT uptake inhibitors on particular symptoms, such as anxiety or retardation. The evidence for a relationship between anxiety and 5-HT has been supported by Banki (1977), Ågren (1981), and Rydin *et al* (1982) and suggests the new selective 5-HT uptake inhibitors are effective in treating anxiety syndromes. Subgroup analyses from studies by Norton *et al* (1984) found fluvoxamine was more effective than imipramine in treating anxiety in patients with severe depression. Moreover, the potent, though not selective, 5-HT uptake inhibitor clomipramine was also found to be effective with respect to anxiety syndromes (Wålinder *et al*, 1976; Thorén *et al*, 1980*a*).

Those selective drugs do not appear to differ from standard tricyclics with regard to their effect on anxiety symptoms in depression. However, our study with zimelidine showed an early effect on anxiety symptoms but concluded that after 4 weeks of treatment, no differences between zimelidine and desipramine were evident with respect to their effects. Moreover, subgroup analyses by Norton *et al* (1984) showed that, for patients with severe depression, fluvoxamine had a better effect on anxiety than did imipramine.

5-HT uptake inhibitors may have effects on other syndromes. Zimelidine was demonstrated to be effective against phobic anxiety by Koczkas *et al* (1981) and against panic syndrome by Evans *et al* (1986). Perse *et al* (1987) reported fluvoxamine was effective in obsessive–compulsive disorder. Fluoxetine was also found to be effective in all seven patients with obsessive–compulsive disorder studied by Fontaine & Chouinard (1986), whereas White *et al* (1986) cited the efficacy of citalopram in a patient with the disorder.

Zak *et al* (1988) examined preliminary data that supported the role of the serotonergic system in the modulation or genesis of obsessive–compulsive disorder. Significant symptomatic relief was reported in patients diagnosed with obsessive–compulsive disorder who were treated with a potent 5-HT uptake inhibitor. Various studies indicate 5-HT uptake inhibitors are more efficacious in treatment than are other psychotropic medications, although the response rate is not as impressive as that found in patients with major depressive illness and/or panic disorder. Thorén *et al* (1980*b*) suggest the antiobsessive effect of clomipramine may be related to its capacity to inhibit 5-HT uptake. Further study is clearly indicated.

Research evaluating the use of selective 5-HT uptake inhibitors in the treatment of panic disorder and comparing them with other types of antidepressant agents is currently being carried out. Sheehan *et al* (1988) reviewed evidence that suggested 5-HT uptake inhibitors are effective in treating panic disorder. The mechanism behind this efficacy, however, is still unclear.

Before its withdrawal from the market, zimelidine was found useful in a study of the treatment of agoraphobia with panic attacks. When compared with imipramine in a double-blind, placebo-controlled study (Evans *et al*, 1986) zimelidine — but not imipramine — was found superior to placebo.

Food intake

Some association between 5-HT and carbohydrate craving, and between carbohydrate craving and specific mood disorders such as premenstrual syndrome (PMS) and seasonal affective disorder (SAD), has been detailed (Wurtman, 1988). Heym & Koe (1988) reviewed the animal studies that suggested serotonin acts to suppress certain feeding behaviours. In clinical studies with 5-HT uptake it has been reported that zimelidine did not have a weight gain effect (Coppen *et al*, 1979; Åberg-Wistedt 1982*a*). In addition a decrease in body weight in obese non-depressed women was found by Simpson *et al* (1981).

The similar effect on weight was observed with fluoxetine as well as during antidepressant treatment and in non-depressed obese humans (Silverstone, 1986; Montgomery *et al*, 1988; Cooper, 1988).

Summary

5-HT Uptake inhibitors seem to produce similar antidepressant effects when compared to standard tricyclics. Their side-effects, primarily nausea and insomnia differ from those of the tricyclics, which are principally anticholinergic effects, sedation, and weight gain. Despite those adverse effects, their pharmacodynamic characteristics make the 5-HT uptake inhibitors suitable for long-term treatment and for treatment of elderly patients.

Further studies are indicated to determine the possible specificity of 5-HT uptake inhibitors for both acute and long-term treatment, particularly for patients not responding to standard antidepressants. Because as many as 25–35% of all patients do not respond to standard antidepressants, the usefulness of these studies can hardly be overemphasised.

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Reduction of Food Intake by Manipulation of Central Serotonin

Current Experimental Results

S. GARATTINI, T. MENNINI and R. SAMANIN

Serotonergic anorectics are correctly defined only if they enhance 5-HT transmission and have their anorectic effects inhibited by drugs that block 5-HT receptors. Fenfluramine, the prototype indirect 5-HT agonist, and its metabolite, norfenfluramine, act as 5-HT releasers and uptake inhibitors and are both more effective in the dextro form. They lack the stimulant activity and do not cause hyperthermia or stereotypical behaviour as is characteristic of amphetamines. The anorectic effect of those drugs is attenuated by metergoline, a 5-HT receptor antagonist, in animals and man; 5-HT uptake inhibitors such as fluoxetine, zimelidine, SL 810385, and sertraline also cause anorexia, but only sertraline antagonism by metergoline has been reported. The effect of serotonergic anorectics on 5-HT release has been poorly investigated. Quipazine and RU-24969 cause anorexia by acting directly on 5-HT post-synaptic receptors. Serotonergic nerve terminals take up $[^3H]$-D-fenfluramine and bind with high affinity in rat brain; uptake, an active process, appears to occur at a different site than binding, which is not affected by ouabain or low temperature. Anorexia is probably induced by interaction with 5-HT$_{1B}$ receptors in the rat; the human equivalent of this receptor is not known, but the 5-HT$_{1D}$ type is a likely candidate.

Changes of mood and affective states are frequently associated with changes in feeding behaviour, the extremes of food intake changes being anorexia nervosa and bulimia nervosa. In recent years considerable progress has been made in understanding brain functions, particularly the complex systems of chemical mediators that make possible transmission or modulation of nerve impulses. At the same time, the development of drugs with a fair degree of specificity for given neurotransmitters has permitted more detailed analysis of brain activity.

Particular progress has been made in understanding the role of 5-hydroxytryptamine (5-HT, or serotonin) for which various types and subtypes of receptors have recently been identified and described (Bradley *et al*, 1986; Peroutka, 1988). Some chemicals, such as fenfluramine, that act on 5-HT are used therapeutically for the control of food intake, whereas others are used to explore serotonergic functions in man (see Murphy *et al*, Meltzer, and Cocarro *et al* elsewhere in this issue). It is particularly interesting that some drugs capable of inhibiting 5-HT uptake have dual therapeutic effects. Sertraline and fluoxetine, for example, act as both anorectics and antidepressants.

This review reports on the progress of current research on serotonergic agents capable of controlling food intake. Their mechanism of action (particularly that of the prototype agent, D-fenfluramine) will be discussed primarily in relation to 5-HT, although it is clear that 5-HT interacts with a number of other chemical transmitters, such as monoamines and peptides, in the brain.

Serotonergic anorectics

The serotonergic anorectics may be considered a new therapeutic class of drug. They may replace the classic amphetamine-like compounds because they have no central stimulatory effects and lack the potential for abuse. All serotonergic anorectics share two characteristics: they enhance 5-HT transmission by acting at multiple levels of the serotonergic system (uptake, release, and receptors) and their anorectic effect must be inhibited by drugs that prevent their direct or indirect action on 5-HT receptors (Garattini & Samanin, 1976; Garattini, 1981; Samanin & Garattini, 1982; Samanin, 1983). At present serotonergic anorectics can be divided into two distinct groups: indirect and direct 5-HT agonists.

Indirect 5-HT agonists

As previously mentioned, fenfluramine is the prototype of the indirect 5-HT agonists. Fenfluramine (see chemical structure in Fig. 1) was originally used in the racemic form, but it was subsequently found that most of the anorectic activity resides in the D form (Garattini *et al*, 1979). D-Fenfluramine is more specific for the serotonergic system (Garattini *et al*, 1979, 1986), whereas the L form has antidopaminergic activity

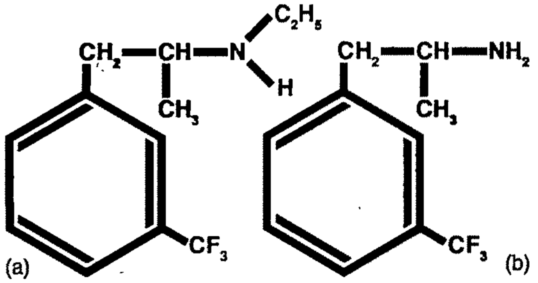

FIG. 1 Chemical structures of (a) D-fenfluramine and (b) metabolite D-nonfenfluramine.

through a mechanism that does not involve direct blockade of dopaminergic receptors (Bettini *et al*, 1987). Interestingly enough, the anorectic activity of L-fenfluramine at relatively high doses is not antagonised by metergoline (Garattini *et al*, 1986), whereas that of D-fenfluramine is.

Any discussion on the mechanism of action of fenfluramine in the D or L form must take into account the formation of an active metabolite, D-norfenfluramine. The product of *N*-deethylation, D-norfenfluramine, is in fact more active than D-fenfluramine in reducing food intake: the ED$_{50}$ for D-norfenfluramine is 0.8 mg/kg i.p., versus 1.29 mg/kg i.p. for D-fenfluramine (Garattini *et al*, 1979).

Reviews on the pharmacology of D-fenfluramine are already available (Garattini *et al*, 1979, 1986; Garattini, 1981, 1987). Therefore, comments here will be limited to recalling that D-fenfluramine differs from D-amphetamine in that not only does D-fenfluramine lack stimulating activity and not cause hyperthermia or stereotypical behaviour, but also the spectra of activity on various kinds of hyperphagia attained experimentally in rats differ as well (Table I). Another anorectic agent, CM57373 (4 amino-6-bromo-2 pyridil-1-piperidine hydrochloride), like D-fenfluramine, enhances serotonergic transmission by acting both as a releaser of 5-HT and as an inhibitor of 5-HT uptake (Miranda *et al*, 1988).

Another way to enhance serotonergic transmission is to prevent 5-HT uptake, and potent and selective 5-HT uptake inhibitors have shown anorectic activity. Among that group of agents if fluoxetine, zimelidine (Samanin, 1983; Blundell, 1984; Garattini *et al*, 1986), sertraline (Dr B. K. Koe, personal communication), and SL 810385 (Angel *et al*, 1988). However, the relationship between the degree of 5-HT uptake inhibition and the decrease of food intake is not clear. We have found indalpine (LM 5008), a highly selective 5-HT uptake inhibitor, lacks the capacity to release 5-HT or to displace it from binding sites (even at doses 27 times the ED$_{50}$ for inhibiting 5-HT uptake *in vivo*), and fails to reduce food intake significantly in rats fasted overnight and trained to eat their food at a fixed time (Samanin *et al*, 1980*a*). On the other hand, Angel *et al* (1988) reported more recently anorectic activity for indalpine at a dose that apparently causes 50% inhibition of 5-HT uptake in rat hypothalamus. It is therefore possible the conditions under which feeding is measured are important for revealing the anorectic effect of 5-HT uptake inhibitors.

The biochemical effects of some 5-HT inhibitors have not yet been well characterised. For instance, fluoxetine's mechanism of action can not be discussed without considering that the available compound is the

TABLE I

Comparison of D-fenfluramine (dF) and D-amphetamine (dA) on a spectrum of experimentally induced hyperphagias in rats

Type of hyperphagia	*dF*	*dA*	*Reference*
Starved rats	+	+	Garattini *et al* (1979)
Palatable food (sated rats)	+	++	Borsini *et al* (1985)
Motivated food eating (runway test)	+	—	Thurlby *et al* (1985)
Tail pinch (sated rats)	++	—	Antelman *et al* (1979)
Insulin glucoprivation	++	—	Carruba *et al* (1985)
Muscimol (dorsal raphe)	+	—	Borsini *et al* (1983)
Neuropeptide y (paraventricular nucleus hypothalamus)	++	+	Bendotti *et al* (1987)

++ = very active; + = active; — = inactive.

racemate and the D and L isomers may have different pharmacological characteristics. Furthermore, fluoxetine is metabolised to norfluoxetine, a metabolite that has biological activity (Table II). Concentrations of norfluoxetine in the brain exceed levels of fluoxetine severalfold after administration of the parent drug (Caccia, unpublished data). That observation may have consequences in the mechanism of action of fluoxetine.

Table II shows the inhibition exerted by fluoxetine isomers and metabolites on synaptosomal 5-HT and D-fenfluramine uptake. 5-HT Uptake is inhibited by fluoxetine at concentrations 40 times lower that needed to inhibit the uptake of D-fenfluramine. However, that ratio is only 6:1 for norfluoxetine. In addition, the activities of fluoxetine and norfluoxetine on 5-HT release are not different from those of D-fenfluramine and D-norfenfluramine. Although it is unclear whether fluoxetine and its metabolite release 5-HT from the granular or the extragranular pool, those data cast doubt on the specificity of fluoxetine as a 5-HT uptake inhibitor *in vivo*.

Considering these observations, the basic mechanisms of interaction of the indirect 5-HT agonists with 5-HT demand more precise characterisation.

Direct 5-HT agonists

Because enhancement of serotonergic transmission leads to a decrease of food intake, chemicals acting on 5-HT post-synaptic receptors should be effective as anorectic agents. We have previously established that several 5-HT agonists, including quipazine (Samanin *et al*, 1977), *m*-chlorophenylpiperazine (Samanin *et al*, 1979) and RU-24969 (Bendotti & Samanin, 1987), reduce food intake by a 5-HT-dependent mechanism. Table III shows the effects of those three agents on 5-HT uptake and release on various receptor types and subtypes. Although it is not completely clear which 5-HT receptor subtypes mediate anorectic activity, a feature common to all three seems to be high affinity for the 5-HT$_{1B}$ receptors, a subtype not yet found in humans (Hoyer *et al*, 1986).

Mechanism of action of D-fenfluramine

In vitro studies have indicated D-fenfluramine is a powerful and relatively selective inhibitor of 5-HT uptake (Borroni *et al*, 1983) in addition to having activity, albeit somewhat less, on the release of granular 5-HT (reserpine-sensitive pool) (Mennini *et al*, 1981). The effect of D-fenfluramine is real and does not depend on its ability to release 5-HT; in fact, it still very actively inhibits synaptosomal 5-HT uptake in conditions (reserpine pretreatment) that completely abolish its 5-HT-releasing activity (Borroni *et al*, 1983). 5-HT Uptake is inhibited and release increased as well with D-norfenfluramine, the principal metabolite of D-fenfluramine in the brain. However, D-norfenfluramine differs from D-fenfluramine in that it is more active on release, particularly on the extragranular 5-HT pool (reserpine-insensitive).

The direct effects of D-fenfluramine and D-norfenfluramine on the binding of various ligands to 5-HT receptors and their subtypes are relatively minor. Similarly, negligible affinity is shown by D-fenfluramine and D-norfenfluramine for catecholaminergic receptors (Garattini *et al*, 1987).

TABLE II

Neurochemical effects of D-fenfluramine, fluoxetine, and their nor-metabolites

Biochemical parameter	*dF*	*dNF*	*(±) Fluox*	*(±) N-Fluox*	*(+) Fluox*	*(—) Fluox*
^{3}H-5-HT uptake IC$_{50}$	0.5	1.4	0.07	0.5	0.09	0.5
^{3}H-DA uptake IC$_{50}$	20.0	17.0	4.5	2.9	3.9	5.2
^{3}H-5-HT release SC$_{25}$	3.2	3.7	2.2	2.0	—	—
^{3}H-dF uptake IC$_{50}$	0.2	3.9	3.0	4.0	2.7	3.9
^{3}H-dF binding IC$_{50}$	0.04	0.5	0.05	0.6	0.03	0.1
^{3}H-paroxetine binding IC$_{50}$	10.0	—	0.02	0.05	0.02	0.04

Figures are expressed as μmol.

IC$_{50}$ = concentration causing 50% inhibition; SC$_{25}$ = concentration causing 25% stimulation.

^{3}H-5-HT uptake and release and ^{3}H-DA uptake were measured as described by Mennini *et al* (1987).

^{3}H-dF binding was measured as described by Mennini *et al* (1988).

^{3}H-paroxetine was measured according to Habert *et al* (1985).

^{3}H-dF uptake was measured by incubating rat brain synaptosomes with 50 nmol ^{3}H-dF for 5 min at 30°C. Passive diffusion was measured at 0°C.

TABLE III

Effect of some 5-HT agonists on 5-HT uptake, release, and receptor subtypes

Biochemical parameter	*Quipazine*	*mCPP*	*RU 24969*
^{3}H-5-HT uptake IC_{50}	0.37	1.30	0.80
^{3}H-5-HT release SC_{25}	10.00	>10.00	—
5-HT_1 receptors IC_{50}	1.00	0.12	0.02
5-HT_{1A} receptors IC_{50}	2.80	0.27	0.005
5-HT_{1B} receptors IC_{50}	0.38	0.14	0.008
5-HT_{1C} receptors IC_{50}	0.023	0.089	0.30
5-HT_2 receptors IC_{50}	1.40	0.40	4.00
5-HT_3 receptors IC_{50}	0.001	0.050	—

^{3}H-5-HT uptake and release were described by Mennini *et al* (1981).
Data are means of four replications differing less than 10%.
5-HT receptor binding was determined using the following ligands: ^{3}H-5-HT cortex (5-HT_1), ^{3}H-8-OH-DPAT hippocampus (5-HT_{1A}), ^{3}H-5-HT striatum (5-HT_{1B}), ^{3}H-spiperone in cortex (5-HT_2).
Data for 5-HT_{1C} and 5-HT_3 receptors are from Hoyer *et al* (1985) and Kilpatrick *et al* (1987), respectively.
SC_{25} are the drug concentrations (μmol) stimulating ^{3}H-5-HT release by 25%; IC_{50} are the drug concentrations (μmol) inhibiting binding by 50%.

Simultaneous inhibition of uptake and stimulation of 5-HT release by D-fenfluramine and D-norfenfluramine should enhance serotonergic transmission synergistically by making more 5-HT available at the post-synaptic receptors. Four research studies suggest that may be the case: the increase of extracellular 5-hydroxyindoleacetic acid (5-HIAA) at short times, shown in experiments utilising voltammetric techniques (De Simoni *et al*, 1988); the increase of extracellular 5-HT, as shown in experiments utilising the microdialysis technique (Schwartz *et al*, 1989); the compensatory reduction of 5-HT synthesis *in vivo* as shown by the method of inhibiting 5-hydroxytryptophan decarboxylase (Invernizzi *et al*, 1986); and the downregulation of 5-HT receptor density in the cortex after repeated treatment with D-fenfluramine (Samanin *et al*, 1980*b*). It should be noted that the number of 5-HT_2 and 5-HT_1, but not 5-HT_{1A} receptors labelled by the ligand [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]-8-OH-DPAT), is decreased after repeated D-fenfluramine treatment (Mennini, unpublished data).

D-Fenfluramine causes a marked, long-lasting reduction of brain 5-HT and 5-HIAA, particularly in telencephalic areas (Garattini *et al*, 1986). The mechanism of that effect is not completely clear but entry of D-fenfluramine into the nerve terminals appears to be a prerequisite (Clineschmidt *et al*, 1978). Receptor stimulation may contribute partially to the depleting effect soon after injection, since 5-HT antagonists partially prevent the drop in 5-HT concentrations (Invernizzi *et al*, 1982).

No effects on brain catecholamine levels, metabolism, or synthesis have been found with anorectic doses of D-fenfluramine (Garattini *et al*, 1986; Invernizzi *et al*, 1986). That is in contrast to the action of amphetamine-like anorectics, which affect brain catecholamines and their metabolites without affecting brain 5-HT and 5-HIAA (Garattini *et al*, 1978).

Binding and uptake of [^{3}H]-D-fenfluramine to brain structures

Binding sites for [^{3}H]-D-fenfluramine have recently been found in the brain, and it appears that brain synaptosomes take up [^{3}H]-D-fenfluramine by an active transport mechanism. Although those two biochemical aspects of D-fenfluramine action have been characterised, their significance for the drug's pharmacological effects requires further study.

Binding of [^{3}H]-D-fenfluramine

High-affinity [^{3}H]-D-fenfluramine binding has been characterised (Mennini *et al*, 1988) in rat brain membranes incubated at 37°C for 90 min in 50 mmol Tris HCl buffer, pH 7.4, containing 0.1% ascorbic acid. Specific binding determined in the presence of 10 μmol unlabelled D-fenfluramine was saturable with a K_d of 80.75 ± 16.09 nmol and B_{max} of 32.40 ± 12.80 pmol/g brain (see Table IV). In the presence of 50 mmol phosphate buffer, the affinity of [^{3}H]-D-fenfluramine is significantly higher (K_d 35.4 ± 4.2 nmol) while the B_{max} remains the same.

TABLE IV

Binding and uptake of dF and 5-HT to brain structures

Biochemical parameter	*^{3}H-dF*	*^{3}H-5-HT*
Binding to brain membranes		
K_d μmol	0.08	0.002
B_{max} pmol/g brain	32.4	15
Uptake by brain synaptosomes		
K_m μmol	0.257	0.080
V_{max} pmol/min/g brain	46	86

^{3}H-5-HT uptake and binding were measured as described by Mennini *et al* (1987).
^{3}H-dF binding was measured as described by Mennini *et al* (1988).
^{3}H-dF uptake was measured as indicated in Table II.
Coefficients of variations are lower than 20%.

The regional distribution of [^{3}H]-D-fenfluramine binding, studied by quantitative autoradiography, showed highest levels in the dorsal raphe (46 fmol/mg tissue). In some slices, intense labelling could be seen in unidentified areas of the brain-stem (60–70 fmol/mg tissue). In the hippocampus [^{3}H]-D-fenfluramine binding was clearly localised in the pyramidal cell layer (20 fmol/mg tissue), whereas binding was diffuse in the thalamus and hypothalamus (15 fmol/mg tissue). Levels were lower in cortex and caudate (10 fmol/mg tissue) and cerebellum (5–10 fmol/mg tissue).

[^{3}H]-D-Fenfluramine binding was reduced more than 15% by 5,7-dihydroxytryptamine (5,7-DHT) lesion in all brain regions examined (except dorsal raphe and cerebellum): hippocampus and thalamus (35%), caudate (25%), hypothalamus (22%), and cortex (18%) (see Table V). [^{3}H]-D-Fenfluramine binding was also reduced by 6-hydroxydopamine lesion, although only in the thalamus (40%), caudate (38%), and hypothalamus (25%).

Pharmacological characterisation showed [^{3}H]-D-fenfluramine binding in 50 mmol phosphate buffer was stereospecific and was displaced by the metabolite, D-norfenfluramine, with high affinity (IC_{50} 530 nmol). Among other good inhibitors of [^{3}H]-D-fenfluramine binding, fluoxetine (IC_{50} 54 nmol) and imipramine (IC_{50} 400 nmol) were among the most active, together with other tricyclic 5-HT uptake inhibitors and indalpine (IC_{50} 124 nmol). Among the negative compounds are a number of dopaminergic drugs, including D-amphetamine (IC_{50} > 10 000 nmol).

Because of imipramine's high affinity for [^{3}H]-D-fenfluramine binding sites, there was interest in investigating further possible analogies and differences. [^{3}H]-D-fenfluramine and [^{3}H]-imipramine binding sites differ in several ways. [^{3}H]-Imipramine binding is enhanced by sodium (Briley & Langer, 1981), whereas [^{3}H]-D-fenfluramine binding is inhibited dose-dependently (5–120 mmol) by NaCl added *in vitro*, with an IC_{50} of about 5 mmol (Mennini *et al*, 1988). Perhaps the most important difference is evident with regard to the nanomolar affinity of 5-HT for a component of [^{3}H]-imipramine binding (Gobbi *et al*, 1988) and the very low affinity (IC_{50} > 460 μmol) of this monoamine (5-HT) for [^{3}H]-D-fenfluramine binding sites. In addition, midalcipran showed high affinity for [^{3}H]-imipramine binding but is inactive on [^{3}H]-D-fenfluramine binding (see Table VI).

It would be interesting to establish whether the stereospecific binding of [^{3}H]-D-fenfluramine to brain structures is related to the biochemical or functional effects of D-fenfluramine. The general conclusion is no relationship exists between such binding and the effect of various anorectic drugs (Garattini *et al*, 1988). In fact, small changes in the ED_{50} for reducing food intake are paralleled by a wide range of concentrations — more than 1000 times — needed to inhibit [^{3}H]-D-fenfluramine binding. However, it is quite possible that only agents acting as indirect 5-HT agonists are recognised by [^{3}H]-D-fenfluramine binding sites. Several agents with that mechanism, such as fluoxetine and *p*-chloroamphetamine, do displace [^{3}H]-D-fenfluramine.

In addition, several agents that counteract the depleting effect of fenfluramine on brain 5-HT, such as chlorimipramine (Ghezzi *et al*, 1973), fluoxetine (Fuller *et al*, 1978), and indalpine (Samanin *et al*, 1980c), also inhibit [^{3}H]-D-fenfluramine binding (IC_{50} for those three compounds being 372 nmol, 51 nmol,

TABLE V

Effect of 5-HT pre-synaptic degeneration by 5,7-DHT on dF binding and dF and 5-HT uptake

Brain area	*^{3}H-dF binding^1*	*^{3}H-dF uptake^1*	*^{3}H-5-HT uptake^1*
Hypothalamus	22 ± 6	47 ± 9	63 ± 7
Hippocampus	35 ± 23	52 ± 11	66 ± 8
Striatum	25 ± 7	45 ± 10	46 ± 3
Cerebral cortex	18 ± 3	25 ± 5	43 ± 14

1. Percentage decrease ± s.d. in 5,7-DHT lesioned brains compared to control brains. See Table IV for details.

TABLE VI

Comparison of ^{3}H-IMI and ^{3}H-dF binding, ^{3}H-dF binding and uptake, and relation to ^{3}H-5-HT uptake

	K_i μmol			
Compound	*^{3}H-dF uptake*	*^{3}H-dF binding*	*^{3}H-IMI binding*	*^{3}H-5-HT uptake*
D-Fenfluramine	0.20	0.031	3.29	0.53
Imipramine	0.25	0.31	0.01	0.12
Serotonin	0.42	>467	0.25	0.08
Indalpine	2.38	0.093	0.001	0.002
Midalcipran	8.89	164	0.05	0.10
Fluoxetine	6.97	0.04	—	0.07
D-Norfenfluramine	3.38	0.42	34.6	0.70
L-Fenfluramine	12.65	0.08	27.0	4.50
Chlorimipramine	1.18	0.29	—	0.02

For ^{3}H-IMI binding, K_i values were calculated from Gobbi *et al* (1988) and those for ^{3}H-5-HT uptake from Mennini *et al* (1985).

and 124 nmol, respectively). Chlorimipramine also partially prevents the anorectic effect of fenfluramine (Ghezzi *et al*, 1973). Those findings, together with the fact that brain concentrations after an anorectic dose of either D-fenfluramine or D-norfenfluramine are high enough to saturate the [^{3}H]-D-fenfluramine binding sites (Mennini *et al*, 1985), suggest those sites may mediate the pharmacological activities of D-fenfluramine and D-norfenfluramine.

[^{3}H]-D-Fenfluramine uptake

[^{3}H]-D-Fenfluramine is actively taken up by brain synaptosomes, with K_m 257±93 nmol and V_{max} 46±14 pmol/min/g wet weight (Table IV). That uptake is prevented by 5-HT uptake inhibitors (Table VI) and by tryptoline, a putative endogenous ligand at imipramine binding sites (IC_{50} 8.1 μmol), but not by nomifensine, an inhibitor of catecholamine uptake. Desipramine showed an IC_{50} of 0.537 μmol. The K_m value for [^{3}H]-D-fenfluramine is in the range of its K_i for inhibition of [^{3}H]-5-HT uptake (530 nmol, Table VI), thus suggesting active uptake of [^{3}H]-D-fenfluramine may utilise the serotonin carrier.

As summarised in Table V, [^{3}H]-D-fenfluramine uptake is markedly reduced by the serotonergic neurotoxin, 5,7-dihydroxytryptamine, further confirming that [^{3}H]-D-fenfluramine is taken up by serotonergic nerve terminals. The degree of reduction of [^{3}H]-D-fenfluramine uptake is similar to the degree of inhibition of [^{3}H]-5-HT uptake in the brain regions studied. However, the V_{max} of [^{3}H]-serotonin uptake in rat brain synaptosomes is about twice that for [^{3}H]-D-fenfluramine uptake. Therefore, either only a portion of 5-HT uptake sites are shared by D-fenfluramine, or the stoichiometries of the transport processes are different.

Like [^{3}H]-D-fenfluramine binding, uptake of that same compound is prevented by drugs that counteract its biochemical and behavioural effects, such as chlorimipramine, indalpine, and fluoxetine (Table VI).

[^{3}H]-D-Fenfluramine binding and uptake occur at different sites

The fact that uptake and binding of [^{3}H]-D-fenfluramine in rat brain show similar affinities raises the obvious question of whether the sites are the same. However, several experimental results exclude that possibility.

Uptake of [^{3}H]-D-fenfluramine is an active process and is therefore slowed by lowering the temperature and by the Na/K ATPase inhibitor, ouabain (Mennini, unpublished data). [^{3}H]-D-Fenfluramine binding is not affected by ouabaine or temperature (Mennini *et al*, 1988). In addition, uptake and binding are saturated at different levels, which results in different V_{max} and B_{max} values. The ability of a given drug to inhibit [^{3}H]-D-fenfluramine binding and uptake do not correlate (Table VI). For example, serotonin inhibits [^{3}H]-D-fenfluramine uptake with K_i 0.42 μmol but it is practically inactive on [^{3}H]-D-fenfluramine binding (K_i>467 μmol). Midalcipran does not inhibit [^{3}H]-D-fenfluramine binding but competes for [^{3}H]-D-fenfluramine uptake with K_i 8.8 μmol. In contrast, L-fenfluramine, D-norfenfluramine, and fluoxetine inhibit [^{3}H]-D-fenfluramine binding more effectively than they inhibit uptake.

In conclusion, high affinity [^{3}H]-D-fenfluramine

TABLE VII
Biochemical effects of several 5-HT antagonists

	IC_{50} (μmol)			
Biochemical parameter	*Metergoline*	*Ritanserin*	*Odansetron*	*Xylamidine*
^{3}H-dF binding	2.900	2.800	1.2	—
^{3}H-dF uptake	16.000	—	—	—
5-HT$_1$	0.008	3.100	>10.0	>10.0
5-HT$_{1A}$	0.003	—	>10.0	—
5-HT$_{1B}$	0.001	—	>10.0	—
5-HT$_{1C}$	0.001	0.002	—	—
5-HT$_2$	0.003	0.0006	>10.0	0.005
5-HT$_3$	—	—	0.013	—

^{3}H-5-HT uptake and release were described by Mennini *et al* (1981).
Data are means of four replications differing less than 10%.
5-HT receptor binding was determined using the following ligands: ^{3}H-5-HT cortex (5-HT$_1$), ^{3}H-8-OH-DPAT hippocampus (5-HT$_{1A}$), ^{3}H-5-HT striatum (5-HT$_{1B}$), ^{3}H-spiperone in cortex (5-HT$_2$).
Data for 5-HT$_{1C}$ and 5-HT$_3$ receptors are from Hoyer *et al* (1985) and Kilpatrick *et al* (1987), respectively.
IC_{50} are the drug concentrations (μmol) inhibiting binding by 50%.

binding seems to be different from that of [^{3}H]-imipramine, [^{3}H]-D-fenfluramine uptake, and [^{3}H]-5-HT uptake.

Which 5-HT receptor is important for D-fenfluramine's anorectic activity?

Although D-fenfluramine and its metabolite, D-norfenfluramine, do not interact with high affinity with any one of the 5-HT receptor subtypes in particular, it is important to clarify whether one or more of those receptors is involved in the anorectic activity of 5-HT. A direct answer can be obtained regarding the relative importance of 5-HT$_1$, 5-HT$_2$, and 5-HT$_3$ receptors by comparing the effects of four 5-HT antagonists on the anorectic activity of D-fenfluramine; metergoline, a competitive antagonist of 5-HT receptors (De Blasi & Mennini, 1983) with similar *in vitro* affinity for both 5-HT$_1$ and 5-HT$_2$ receptors; ritanserin, a potent and selective 5-HT$_2$ receptor antagonist (Leysen *et al*, 1985); odasetron, a selective 5-HT$_3$ antagonist (Richardson *et al*, 1985); and xylamidine, a peripherally acting 5-HT antagonist (Table VII).

As shown in Table VIII, only metergoline caused dose-related reduction of the anorectic effect of D-fenfluramine. That was shown in studies of food-deprived rats eating laboratory chow, with complete antagonism at 1 mg/kg, a dose that occupies cortical 5-HT$_2$ receptors by about 50% (Garattini *et al*, 1987; Samanin *et al*, 1989).

TABLE VIII
5-HT antagonists and anorexia by dF in rats

		Food intake (% of untreated controls)	
5-HT antagonist	*mg/kg*	*Saline*	*dF*
None		100	25
Metergoline	0.125	104	34
	0.5	106	72**
	1.0	98	104**
Ritanserin	0.5	120	30
	1.0	100	40*
Odanserin	0.5	109	30
	1.0	90	32
Xylamidine	2.5	100	25

* $P<0.05$.
** $P<0.01$.
See Borsini *et al* (1982) and Samanin *et al* (1989) for details.

Ritanserin, at a dose causing 50% occupation of cortical 5-HT$_2$ receptors (0.5 mg/kg), had no effect on D-fenfluramine anorexia and only partially prevented

D-fenfluramine's anorectic effect at a dose (1 mg/kg) that caused maximal occupation of 5-HT$_2$ receptors (Samanin *et al*, 1989). However, that effect was accompanied by an approximately 50% reduction of the concentrations of D-norfenfluramine in the rat brain; (30 min after D-fenfluramine 2.5 mg/kg i.p., D-norfenfluramine concentrations in the cortex and hypothalamus were 4.5 ± 0.4 and 2.9 ± 0.3 nmol/g ± SEM, as opposed to 2.0 ± 0.3 and 1.3 ± 0.3 in the same brain areas of animals pre-treated with ritanserin 1 mg/kg i.p. 30 min before D-fenfluramine). Thus, the antagonism was presumably due to a metabolic interaction (Samanin *et al*, 1989). Metergoline at fully effective doses did not modify the levels of D-fenfluramine or D-norfenfluramine in the cortex or hypothalamus. Odanserin (0.5 and 1 mg/kg i.p.) did not influence the anorectic effect of D-fenfluramine (Table VIII).

Those results clearly argue against a role of 5-HT$_2$ or 5-HT$_3$ receptors in mediating the anorectic effect of D-fenfluramine and indicate the 5-HT$_1$ receptors as suitable candidates. However, in non-deprived rats trained to eat a palatable diet, ketanserin, a 5-HT$_2$ antagonist, apparently reduced the anorectic effect of fenfluramine (Hewson *et al*, 1988). In rats adapted to a schedule in which a milk diet was presented for 6 h daily, Schechter & Simansky (1988) found dose-related reduction of feeding by a 5-HT$_2$ agonist. That effect was antagonised by ketanserin but not by the peripherally acting 5-HT$_2$ antagonist, xylamidine. Thus, the central 5-HT receptor type involved in fenfluramine anorexia may depend on the nutritional state of the experimental subject or on the quality of food.

The 5-HT$_1$ receptors are not a homogeneous class, but comprise at least four subtypes, 1A, 1B, 1C, and 1D (Peroutka, 1988). Since no antagonists are specific for those receptors, it is difficult at present to experiment with them directly. Nevertheless, it can be excluded that 5-HT$_{1A}$ receptors are involved in the action of D-fenfluramine: 8-OH-DPAT, a selective 5-HT$_{1A}$ agonist, significantly increases food intake at low doses in free-feeding rats. However, it causes anorexia in food-deprived rats at doses (0.5 mg/kg i.p.) associated with a motor syndrome which obviously interferes with eating (Dourish *et al*, 1985*a,b*; Bendotti & Samanin, 1987). Furthermore, "anorectic" doses of 8-OH-DPAT were not antagonised by metergoline, demonstrating that the effects were not 5-HT dependent (Bendotti & Samanin, 1987). The increase of eating caused by 8-OH-DPAT was prevented by intraventricular injections of a 5-HT neurotoxin and could be elicited by injecting 8-OH-DPAT in the midbrain raphe nuclei (Bendotti & Samanin, 1986; Hutson *et al*, 1986), suggesting activation of autoreceptors in serotonergic cell bodies in the midbrain raphe stimulates feeding (Bendotti & Samanin, 1986; Hutson *et al*, 1986). Since activation of 5-HT$_{1A}$ autoreceptors reduces serotonergic transmission, feeding may be elicited by reducing the activity of 5-HT neurons in the brain. Other 5-HT$_{1A}$ receptor agonists such as buspirone have been reported to increase food intake in free-feeding rats (Dourish *et al*, 1986).

The exclusion of 5-HT$_{1A}$ receptors as a target for D-fenfluramine-induced anorexia leaves open the possibility that 5-HT$_{1B}$ receptors may be appropriate candidates. Favouring this conclusion is the fact that in both free-feeding and starved rats, RU 24969, a 5-HT$_{1A}$ and 5-HT$_{1B}$ agonist, has anorectic activity that is antagonised by metergoline (Bendotti & Samanin, 1987). Quipazine and *m*-chlorophenylpiperazine, two anorectic agents whose effects are prevented by metergoline (Samanin *et al*, 1977, 1979), have been reported to have good affinity for 5-HT$_1$ receptors.

Until better, more selective 5-HT antagonists are developed, it can be concluded that increased serotonergic transmission elicited by D-fenfluramine induces anorexia by interacting with 5-HT$_1$ receptors — precisely, with 5-HT$_{1\ \mathrm{non}\ A}$ receptor subtypes.

Central or peripheral action of D-fenfluramine

Since peripherally administered 5-HT induces anorexia (Pollack & Rowland, 1981), it is logical to investigate whether the anorexic effect of D-fenfluramine has a peripheral component. However, the induction of anorexia by D-fenfluramine in food-deprived animals by a peripheral mechanism can be excluded, and two findings specifically justify that conclusion.

First, xylamidine, a potent 5-HT inhibitor that does not cross the blood–brain barrier, prevents 5-HT anorexia but not D-fenfluramine anorexia (Borsini *et al*, 1982). In addition, xylamidine affects neither the anorectic activity of D-norfenfluramine in fasted animals nor the decrease of food intake elicited by D-fenfluramine in sated rats exposed to palatable food (Borsini *et al*, 1982, 1985). Second, ritanserin, a powerful and selective 5-HT$_2$ inhibitor, prevents the anorexia elicited by peripherally — not not centrally — administered 5-HT (Massi & Marini, 1987), indicating that 5-HT$_2$ receptors, probably in the gastrointestinal tract, mediate 5-HT-dependent anorexia in the periphery. As discussed above, ritanserin is inactive on D-fenfluramine anorexia.

Mechanism of action of sertraline

As already mentioned, sertraline is one of the most potent inhibitors of 5-HT uptake, in which its specificity is 20 times that of its inhibition of noradrenaline or dopamine uptake (Heym & Koe, 1988). Like many monoamine uptake inhibitors, sertraline undergoes biochemical transformation via *N* demethylation *in vivo* (see Fig. 1 for chemical structure) to form *N*-desmethylsertraline (Koe *et al*, 1983). However, the metabolite is less potent than the parent compound, although its specificity on 5-HT uptake inhibition is the same (Heym & Koe, 1988), which indicates it contributes very little, if at all, to the overall pharmacological effect of the parent drug. Sertraline causes a dose-dependent decrease of food intake in rats at doses that do not affect other behaviours. Similar to that of D-fenfluramine, sertraline's anorectic activity is blocked by non-selective 5-HT antagonists such as metergoline and methylsergide but is unaffected by the selective 5-HT_2 antagonist, ketanserin. Destruction of central 5-HT nerve terminals induced by 5,7-dihydroxytryptamine reduces the anorectic effect of sertraline, but inhibition of peripheral 5-HT receptors induced by xylamidine has no such effect (Lucki, 1988).

All those study results, when taken as a whole, suggest 5-HT may be involved in sertraline's action on rat food intake.

Effect of serotonergic anorectics in man

Some members of the pharmacological class referred to as serotonergic anorectics have passed the experimental level and have reached clinical applications. For example, fenfluramine, as a racemate, was the first drug of that class used as an anorectic for the treatment of obesity (Pinder *et al*, 1975). It was subsequently found, in agreement with experimental data, that D-fenfluramine was more effective than the racemate in humans in terms of hunger ratings, decrease of food intake (Goodall & Silverstone, 1987), and decrease of body weight (Nathan & Rolland, 1987). A 30-mg oral dose of D-fenfluramine is considered equivalent to 60 mg DL-fenfluramine in that respect, with fewer side-effects (Nathan & Rolland, 1987). It is interesting that metergoline antagonises the action of D-fenfluramine in humans, indicating that the mechanism of action established in rats may also be valid in humans (Silverstone & Goodall, 1987).

Fluoxetine is another drug available for clinical use. Used as an antidepressant agent, it also reduces body weight, whereas the non-serotonergic antidepressants tend to cause weight gain. Similar observations were made for zimelidine and fluvoxamine (Nathan & Rolland, 1987). Fluoxetine (20–60 mg orally) dose-dependently reduced body weight in an 8-week trial (L. R. Levine, European Obesity Meeting, Stockholm, 1988). Fluoxetine at a daily dose of 60 mg was useful in relieving the symptoms of bulimia in a double-blind controlled study (Freeman, 1988). Sertraline reduced body weight in obese patients during an 8-week double-blind controlled trial (D. P. Doogan, personal communication).

Concluding remarks

The class of serotonergic agents that affects food intake is expanding, and the mechanisms involved are gradually becoming clearer, although the precise site(s) of action are still to be elucidated. Indirect serotonergic agonists that block 5-HT uptake and enhance release and direct serotonergic agonists, that presumably act at 5-$HT_{1\ \mathrm{non\ A}}$ receptor subtypes have anorectic activity, whereas 5-HT_{1A} agonists acting on autoreceptors located on 5-HT cell bodies increase food intake. The regulation of food intake by 5-HT is an interesting example of how opposite behaviours may be elicited by different receptor subtypes with a different regional location.

The favourable clinical results achieved with serotonergic anorectic agents will certainly increase their use, not only for therapeutic purposes but also as tools for investigating serotonergic activity in man. That in turn will allow better characterisation of the links between 5-HT and other chemical mediators and hormones and help clarify the role of 5-HT in eliciting physiological and pathological elements of behaviour.

In order to draw suitable conclusions from the use of such tools, it is important to bear in mind their limitations in use in terms of their specificity of action and the possibility of metabolic interactions with other drugs. A continuous effort to better characterise those drugs and to synthesise more specific agents will undoubtedly cast much fresh light on the role of 5-HT on food intake, not only in animals but also in man.

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Central Serotonin and Impulsive Aggression

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The role of central serotonergic (5-HT) system dysfunction in the regulation of aggression in both animals and man has been investigated for more than the past two decades. Evidence for reduced central 5-HT in the mediation of aggression comes from both behavioural and correlative studies. Functional reduction and augmentation of 5-HT activity is respectively associated with increased and decreased aggression in various animal models of aggression. While similar studies in man have not been performed, strong and consistent associations between indices reflecting reduced pre-synaptic 5-HT activity and aggression have been reported. Evidence of post-synaptic receptor upregulation in the brains of suicide victims has also been reported leaving the functional status 5-HT activity in such patients an open question. However, reduced neuroendocrine (i.e. prolactin) responses to fenfluramine, a 5-HT uptake inhibitor/releaser, which activates both pre- and post-synaptic sides of the 5-HT synapse, strongly suggest that overall central 5-HT activity is reduced in mood and/or personality disorder patients with history of suicidal and/or impulsive aggressive behaviour. Preliminary data with the 5-HT receptor agonist *m*-chlorophenylpiperazine further suggest that reduced activity of post-synaptic 5-HT receptors may be an important correlate of impulsive aggressive behaviour. Pharmacological agents with potent 5-HT pre- and/or post-synaptic augmenting effects should be tested clinically to determine their efficacy in the treatment of impulsive aggressive behaviour in psychiatric patients.

The role of the central serotonergic (5-HT) system in behavioural disorders has been a focus of research for more than two decades (for reviews, see Åsberg *et al*, 1987; Meltzer & Lowy, 1987). Through its widespread projections to the cortex and various limbic structures, the 5-HT system is involved in the regulation of a wide variety of physiologic and affective functions, including sleep, appetite, noiciception, cognition, mood, sexual, and other motoric activity (Vogt, 1982). Hence, dysfunction within this system is likely to contribute to the aetiology of any of the various psychiatric disorders that prominently feature abnormalities in these functions (e.g. major affective, anxiety, eating, and personality disorders; Coccaro and Murphy, in press).

Recently, there is recognition that abnormalities within the central 5-HT system may be manifest across diagnostic groups along specific dimensions of behaviour. In particular, evidence that abnormalities of central 5-HT function are associated with impulsive (self- [i.e. suicidal] or other-directed) aggressive behaviour among patients from different diagnostic groups suggests that impulsive aggression may be the most common behavioural correlate of central 5-HT system dysfunction (Åsberg *et al*, 1987). Accordingly, this review will focus on work that reflects the role of the central 5-HT system in the expression of impulsive aggressive behaviour.

Animal studies

Evidence that 5-HT has played a central role in aggressive behaviour has existed in the literature since 1959. At that time 5-HT was first reported to reduce isolation-induced aggression in mice (Yen *et al*, 1959). Subsequently, a wealth of data from animal studies has been published supporting the hypothesis that central 5-HT is integrally involved in the regulation of aggressive behaviour (Soubrie, 1986).

In addition to isolation-induced aggression (a model in which aggressive behavour has been shown repeatedly to correlate inversely with central 5-HT activity (Garattini *et al*, 1969; Valzelli & Bernasconi, 1979), shock-induced fighting (Kantak *et al*, 1981; Sewell *et al*, 1982), muricidal behaviour (Waldbillig, 1979; Katz, 1980) and filicidal behaviour (i.e. pup killing; Copenhaver *et al*, 1978) are each increased and decreased by neurochemical manipulations which, respectively, decrease and increase central 5-HT activity.

Evidence exists that reduced central 5-HT activity is more closely associated with a tendency toward aggressive behaviour, rather than the frank expression of aggression itself. For example, previous exposure of rats to mice prevents the muricidal response to manipulations which reduce central 5-HT activity (Marks *et al*, 1977; Vergnes *et al*, 1977). Those findings suggest that in the absence of sufficient arousal, reduced central 5-HT activity may not be associated with aggression. In a recent study of tryptophan-depleted non-human primates, no aggressive behaviour occurred in the absence of conditions which heightened arousal of the subject (e.g. by insertion of a nasogastric tube; Chamberlain *et al*, 1987). Thus, reduced central 5-HT activity may be more specifically associated with a lowered threshold for aggressive responses to noxious stimuli than with unprovoked aggressive behaviour itself.

Human studies: post-mortem

Pre-synaptic indices

Studies analysing a post-mortem index of pre-synaptic 5-HT function have examined concentrations of 5-HT and/or its metabolite 5-HIAA, or the binding of tritiated imipramine to brain tissue taken from individuals who had committed suicide (Åsberg *et al*, 1987). While it is not generally known if these subjects displayed clinically significant impulsive aggressive behaviour prior to death, some of the individuals had committed suicide by violent means and may have been generally aggressive during their lives.

Small but statistically significant reductions in 5-HT and/or 5-HIAA concentration have been reported in one or more brain areas in six of eleven reports published to date. Reductions in these metabolites have been reported for the brain stem or other brain regions in all six reports (Shaw *et al*, 1967; Bourne *et al*, 1968; Pare *et al*, 1969; Lloyd *et al*, 1974; Beskow *et al*, 1976; Korpi *et al*, 1986) but for the frontal cortex in only one (Beskow *et al*, 1976). Accordingly, while there may be regional differences in 5-HT system abnormalities in the brains of suicide victims, pre-synaptic 5-HT activity in at least the brain stem may be reduced in these individuals.

Similarly, reductions in the maximal binding of tritiated imipramine (^{3}H-IMI: B_{max}) to brain tissue in various brain regions of suicide victims have been reported in four of six studies pubished to date (Stanley *et al*, 1982; Crow *et al*, 1984; Paul *et al*, 1984; Gross-Isseroff *et al*, 1989); no differences were reported in one (Owen *et al*, 1986) while an increase in ^{3}H-IMI: B_{max} was reported in another (Meyerson *et al*, 1982). ^{3}H-IMI is thought to bind to a pre-synaptic 5-HT receptor site associated with the 5-HT transporter (Langer *et al*, 1987) and may reflect some aspect of pre-synaptic 5-HT function. These observations are compatible with those of the monoamine metabolite studies reviewed above and suggest that there may be a structural abnormality in pre-synaptic 5-HT function (e.g. loss of 5-HT-transporter sites; loss of pre-synaptic 5-HT terminals) in individuals displaying serious suicidal behaviour.

Post-synaptic indices

In contrast to those observations, putative indices of increased post-synaptic 5-HT function from brain tissue of suicide victims have been reported. Greater binding of radioligands for the 5-HT$_2$ post-synaptic receptor have been reported as increased in the frontal cortex of suicide victims in four of eight studies published (Arora and Meltzer, 1989; Stanley & Mann, 1983; Ferrier *et al*, 1986; Mann *et al*, 1986); one of the four remaining negative studies noted a small, statistically non-significant increase in 5-HT$_2$ binding sites (Cheetham *et al*, 1988).

This observation is thought to reflect a compensatory response of the post-synaptic 5-HT$_2$ receptor to diminished pre-synaptic activity or innervation. Empirical support for this hypothesis is limited, although an inverse, statistically non-significant ($r = -0.42$, $P>0.20$) relationship between ^{3}H-IMI and 5-HT$_2$ receptor binding sites in the frontal cortex of violent suicide victims has been reported (Stanley & Mann, 1983).

Possibly, increased 5-HT$_2$ receptor binding does not represent a compensatory response to diminished pre-synaptic 5-HT activity in impulsive aggressive and suicidal individuals. Support for this hypothesis includes the observation that depletion of pre-synaptic 5-HT is accompanied neither by an increase in 5-HT$_2$ receptor number (Seeman *et al*, 1980; Blackshear *et al*, 1981; Quik & Azmitia, 1983) nor by an increase in receptor-mediated biochemical responses to 5-HT stimulation (Conn & Sanders-Bush, 1986).

Alternately, if 5-HT$_2$ receptor upregulation is associated with an increase in 5-HT$_2$ subsystem activity, it is possible a decrease in 5-HT$_1$ subsystem activity could result. Recent evidence of reciprocal relationships between 5-HT$_2$ and 5-HT$_1$ receptor-mediated functions (Gudelsky *et al*, 1986), together with data demonstrating simultaneous decreases and increases, respectively, in 5-HT$_2$ and 5-HT$_1$-mediated behavioural responses during antidepressant treatment (Pericic & Manev, 1988), provide preliminary support for this conjecture. Pre-clinical data have suggested a role in the mediation of behavioural inhibition for 5-HT$_1$ rather than 5-HT$_2$ receptor subsystems (McMillen *et al*, 1987). Hence, if 5-HT$_2$ receptor upregulation is a compensatory phenomenon, it is possible that it is secondary to reduced activity within the 5-HT$_1$ system, rather than reduced 5-HT activity within the synapses served by 5-HT$_2$ receptors. Further research with 5-HT receptor-subtype-specific probes will be necessary to resolve these issues.

Human studies: ante-mortem

Pre-synaptic indices

Åsberg *et al* (1987) have reviewed evidence supporting the hypothesis that putative pre-synaptic 5-HT indices are reduced in suicidal behaviour. Reduced cerebrospinal fluid (CSF) concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (CSF 5-HIAA) have also been reported in most clinical studies of patients (regardless of psychiatric diagnosis) who have attempted suicide prior to study. These data strongly support the notion that vulnerability to commit a suicidal act is related to reduced pre-synaptic 5-HT activity. However, as suicidal behaviour is often related to aggressive behaviour in general (Brown *et al*, 1982; Berglund, 1984), these data also raise the possibility that low concentrations of 5-HIAA in cerebrospinal fluid are inversely related to vulnerability to respond aggressively to adverse stimuli.

To date, at least 13 studies investigating the relationship between pre-synaptic indices of 5-HT function in aggressive behaviour have been reported. Nine utilise levels of 5-HIAA in cerebrospinal fluid as a central 5-HT index (Table I) and four utilise whole blood 5-HT, plasma tryptophan (the 5-HT precursor), or ^{3}H-IMI binding to the platelet as a peripheral 5-HT index (Table II).

Nearly all studies show that concentrations of CSF 5-HIAA are inversely related to clinician- or self-reported ratings of aggression (Brown *et al*, 1979, 1982; Linnoila *et al*, 1983a; Lidberg *et al*, 1985); irritability and hostility (Rydin *et al*, 1982; Brown & Goodwin, 1984; van Praag, 1986; Roy *et al*, 1988), or criminal activity (Linnoila *et al*, 1983a; Lidberg *et al*, 1985; van Praag, 1983; Virkkunen *et al*, 1987) (Table I). CSF 5-HIAA has also been found to correlate inversely with self-rated behavioural difficulties during childhood (Brown *et al*, 1985), raising the possibility that reduced 5-HT activity during childhood and adolescence may have also been associated with behavioural difficulties during that time.

Even peripheral indices of 5-HT function may correlate with aggressive behaviours in some clinical populations. Three of four studies examining a peripheral index of 5-HT function (Table II) have demonstrated an inverse relationship with clinician-rated measures of aggression, reflected either as a measure of current behaviour (Greenburg & Coleman, 1976; Stoff *et al*, 1987) or as the historic occurrence of a serious aggressive act (e.g. leading to incarceration; Branchey *et al*, 1984). While a positive correlation between whole blood 5-HT and conduct disorder ratings in adolescent males was reported in the most recent study Pliszka *et al*, 1988), there is preliminary evidence that whole blood 5-HT varies inversely with other central indices of 5-HT function (McBride *et al*, 1989). Further investigation into the pathophysiologic significance of such findings is necessary. Whether (and how) these indices mirror processes occurring in the relevant areas of the brain, as proposed for platelet ^{3}H-IMI binding, or represent peripheral factors that play a role in regulating the disposition of 5-HT in the brain, as proposed for the plasma tryptophan/amino acid ratio, remains to be determined.

Post-synaptic indices

While there are no data available examining the relationship between an index of post-synaptic 5-HT function and impulsive aggression in clinical samples, a positive relationship between the cortisol response to 5-HTP challenge and history of suicidal behaviour in 40 depressed and manic patients has been reported (Meltzer *et al*, 1984). This finding, like that of increased 5-HT$_2$ receptor binding in the brains of suicide victims reviewed above, has been interpreted as reflecting post-synaptic receptor upregulation in response to diminished pre-synaptic 5-HT (Meltzer *et al*, 1984). However, while the cortisol response to 5-HTP challenge has been shown to reflect activation at 5-HT synapses in general (Petraglia *et al*, 1984) these responses do not appear to reflect activity at 5-HT$_2$ post-synaptic receptors specifically (Facchinetti *et al*, 1987). Further investigation with more selective and specific post-synaptic 5-HT receptor probes will be necessary to resolve the functional state of the post-synaptic 5-HT receptors in these largely bipolar patients.

Integrated pre-synaptic and post-synaptic indices

Evidence of reduced pre-synaptic 5-HT activity and increased 5-HT receptor binding or neuroendocrine responsiveness to 5-HTP challenge in aggressive and suicidal patients points to a reduction in overall 5-HT activity in those patients. In this model, increased indices of post-synaptic 5-HT receptor activity (Stanley & Mann, 1983; Ferrier *et al*, 1986; Mann *et al*, 1986) represent a compensatory response to reduction in pre-synaptic 5-HT activity. Presumably, the compensatory mechanisms at the post-synaptic site are insufficient, and overall 5-HT activity is reduced. However, because no study to date has employed a methodology capable of assessing simultaneous pre- and post-synaptic 5-HT activity, the actual state of overall 5-HT function in patients with impulsive aggression or histories of suicide attempt is unknown. To address this issue, Coccaro *et al* (1989) examined the prolactin (PRL) response to fenfluramine in patients with mood and/or personality disorders.

Fenfluramine increases 5-HT system activity at 5-HT synapses by releasing endogenous stores of 5-HT and by blocking its reuptake into the pre-synaptic terminal (Rowland & Carlton, 1986). The burst of released 5-HT by acute challenge with fenfluramine then stimulates the post-synaptic 5-HT receptor and leads to a variety of post-synaptically mediated events which, in the hypothalamic-pituitary axis, lead to the release of anterior pituitary hormones such as prolactin (Quattrone *et al*, 1983; Lewis & Sherman, 1985). Fenfluramine-induced release of prolactin is antagonised by 5-HT

TABLE I

Clinical psychobiologic studies regarding indices of central 5-HT function and impulsive aggressive behaviour

Study	*Patient group*	*5-HT index*	*Result**
Brown *et al* (1979)	24 male naval recruits DSM-II personality disorder	CSF 5-HIAA	Inverse correlation with life history of aggressive events ($r = -0.78$)
Brown *et al* (1982)	12 male naval recruits with DSM-III borderline personality disorder (BPD)	CSF 5-HIAA	Inverse correlation with MMPI-Pd scale ($r = -0.77$); trivariate relationship with low CSF 5-HIAA and life history of aggression and suicide attempt
Rydin *et al* (1982)	14 pairs of depressed and/or suicidal patients (6 male/ 8 female pairs) with low and normal CSF 5-HIAA matched for age and body height	CSF 5-HIAA	Low CSF 5-HIAA patients had higher Rorschach ratings for variables related to hostility and anxiety
Linnoila *et al* (1983)	36 male violent offenders with history of alcoholism and DSM-III personality disorder	CSF 5-HIAA	Violent offenders with 'impulsive' personality disorders had lower CSF 5-HIAA than those with a 'non-impulsive' personality disorder; CSF 5-HIAA was lower in patients with history of suicide attempt
Lidberg *et al* (1985)	16 male homicide offenders (5 subjects who had killed a sexual partner; 11 subjects who had killed someone other than a sexual partner)	CSF 5-HIAA	Subjects committing homicide against sexual partner had lower CSF 5-HIAA than those who killed a person other than a sexual partner
Brown *et al* (1985)	12 male naval recruits from Brown *et al* (1979, 1982)	CSF 5-HIAA	Inverse correlation with self-reported behavioural problems during childhood
van Praag (1983)	50 patients with depression; 25 with low CSF 5-HIAA, 25 with normal CSF 5-HIAA	CSF 5-HIAA (Post-probenecid)	Greater frequency of suicide attempt, outward directed hostility and contact with the police in low CSF 5-HIAA group
Virkkunen *et al* (1987)	20 male arsonists	CSF 5-HIAA	Reduced CSF 5-HIAA in 'impulsive' arsonists; inverse correlation with criminal acts other than arson ($r = -0.46$)
Roy *et al* (1988)	17 healthy (10 male/7 female) nonpatient volunteers	CSF 5-HIAA	Inverse correlation with 'acting out' hostility ($r = -0.53$)
Coccaro *et al* (1989)	20 male patients with DSM-III Axis II personality disorder	Prolactin (PRL) response to fenfluramine challenge (60 mg,p.o.): PRL[FEN]	Inverse correlation with 'impulsive aggression' ($r = -0.77$). Affect of this dimension upon PRL[FEN] found to account for the reduced PRL[FEN] responses seen among patients with BPD and histories of suicide attempt and episodic alcohol abuse

* Probability values for reported correlation coefficients are 0.05 (i.e. $P < 0.05$) or lower.

TABLE II

Clinical psychobiologic studies regarding indices of peripheral 5-HT function and impulsive aggressive behaviour

Study	*Patient group*	*5-HT index*	*Result**
Greenberg & Coleman (1976)	30 mentally retarded patients with hyperactivity and aggressive behaviour	Whole blood 5-HT	Inverse relationship with hyperactivity and aggression observed
Pliszka *et al* (1988)	44 adolescent males; 27 at a juvenile detention centre; 17 at a community mental health clinic	Whole blood 5-HT	Positive correlation with conduct ratings (r = 0.53) in sample (n = 43)
Branchey *et al* (1984)	43 male alcoholics	Plasma tryptophan/ neutral amino acid ratio	Tryptophan AA ratio low in alcoholics with history of aggression compared to alcoholics without this history
Stoff *et al* (1987)	17 (14 male/3 female) pre-pubertal children with DSM-III conduct disorder; 15 age/sex matched control children	Platelet ^{3}H-IMI binding (B_{max})	Conduct disorder children low compared to an age-matched group of normal children. Inverse correlation with the aggressive (r = −0.48) and externalizing (r = −0.42) factors of a parent-evaluated assessment in entire sample

* Probability values for reported correlation coefficients are 0.05 (i.e. $P<0.05$) or lower.

receptor blockers (Quattrone *et al*, 1983; Lewis & Sherman, 1985). It may be augmented after long-term destruction of pre-synaptic 5-HT terminals in animal studies (Kuhn *et al*, 1981), indicating that this measure can reflect, to some degree, the sensitivity of the post-synaptic 5-HT receptor. However, because the initial site of action of fenfluramine is pre-synaptic, and can be abolished by acute lesions of pre-synaptic 5-HT terminals (Quattrone *et al*, 1979), PRL responses to fenfluramine are interpreted generally as reflecting the 'net' result of pre- and post-synaptic activation of the 5-HT system in the hypothalamic–pituitary axis (Siever *et al*, 1984; Coccaro *et al*, 1989).

Studies of the fenfluramine challenge in patients with major affective disorder and/or personality disorders (Coccaro *et al*, 1989) reveal that such patients exhibit reduced prolactin responses to fenfluramine compared with normal controls. In patients with a history of suicide attempt, prolactin responses to fenfluramine were reduced in comparison with the patients without this history or to normal controls. However, only those patients with DSM-III axis II personality disorder displayed an inverse correlation between the prolactin response to fenfluramine and 'irritable' impulsive aggression (Fig. 1); neither patients with major affective disorders or normal controls showed any relationship

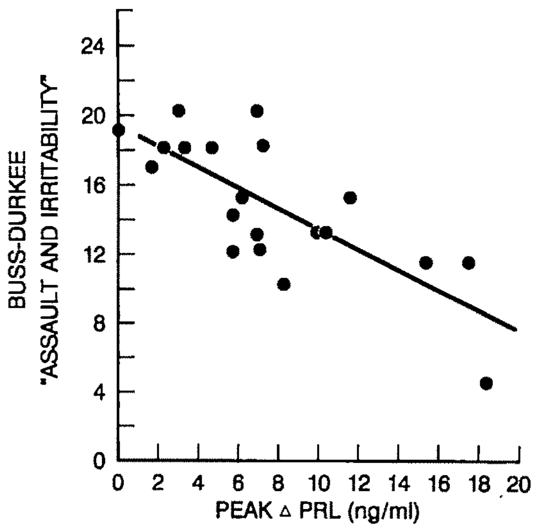

FIG. 1 Correlation between peak delta PRL responses to fenfluramine and the sum score of the self-rated Buss-Durkee 'Assault' and 'Irritability' subscales (from the Buss-Durkee Hostility Inventory; Buss & Durkee, 1957) in 20 male patients with DSM-III personality disorders; $n = 20$, $r = -0.77$, $P = 0.0002$. (Data from Coccaro *et al*, 1989.)

between outwardly directed impulsive aggression and this index of overall 5-HT function. Additionally, patients with histories of bipolarity did not manifest an inverse relationship between history of suicide attempt (i.e. inwardly directed aggression) and prolactin responses to fenfluramine. In the subset with personality disorder, the inverse relationship between prolactin responses to fenfluramine and impulsive aggression appeared to account for reduced prolactin responses to fenfluramine observed among three subgroups of patients: those meeting DSM-III criteria for borderline personality disorder; those defined as having a history of suicide attempt(s); and those with a history of episodic alcohol abuse. Accordingly, the most powerful correlate of overall 5-HT function in these groups appeared to be a history of impulsive aggressive behaviour.

While the prolactin response to fenfluramine cannot specifically locate the pre- and post-synaptic site of this abnormality, preliminary data reveal a similar inverse relationship between prolactin responses to the direct post-synaptic 5-HT receptor agonist, *m*-chlorophenylpiperazine (Mueller *et al*, 1985, 1986), and impulsive aggression in five of the subjects included in our fenfluramine challenge study ($r = -0.87$, $P<0.05$; Coccaro *et al*, unpublished data). This suggests that post-synaptic 5-HT receptor sensitivity may be reduced in such patients and that this abnormality may contribute to the reduced prolactin responses to fenfluramine observed in these patients. However, because the endogenous 5-HT released by fenfluramine may stimulate any number of 5-HT receptor subtypes, it is not known if the diminished PRL responses to fenfluramine are reflecting diminished post-synaptic receptor sensitivity of the 5-HT$_1$ (a,b,c,d), 5-HT$_2$, or 5-HT$_3$ receptor subtype. Further investigation with more selective and specific post-synaptic 5-HT receptor probes will be necessary to uncover which of the many 5-HT receptor subtypes may be subsensitive in these patients.

A psychobiological model of 5-HT function in impulsive aggression: a rationale for the understanding and treatment of impulsive aggression

Overall, the picture that emerges from these data is that reduced indices of 5-HT function correlate most specifically with 'irritable' impulsive aggression, rather than premeditated aggression or violence. The observation that violent subjects (Linnoila *et al*, 1983a) and/or homicidal offenders (Lidberg *et al*, 1985) who commit premeditated acts of aggression toward others have relatively normal concentrations of CSF 5-HIAA suggests that violence by itself is not necessarily associated with reduced 5-HT function. Moreover, most studies of patients with low CSF 5-HIAA find increases in irritability (Brown & Goodwin, 1984) or hostility (Rydin *et al*, 1982; van Praag, 1986; Roy *et al*, 1988) if not histories of actual impulsive (outwardly directed) aggressive acts. This clinical picture is compatible with that observed in animal studies that characterise the central hyposerotonergic state by hyperirritability, hyperexcitability, and hypersensitivity (Valzelli, 1981).

An understanding of how reduced 5-HT function relates to non-premeditated suicidal behaviour follows directly from these observations. Reduced function in the relevant central 5-HT pathways renders the affected individual vulnerable to responding to noxious stimuli in an exaggerated fashion. Hence, the individual strikes out at the source of the noxious stimuli (i.e. arousal), be it the self (e.g. in dysphoric-depressive states) or another stimulus in the environment (e.g. an angry-hostile assault) at a lower threshold. Accordingly impulsive aggressive behaviour may be considered to be the net result of inhibiting (mediated by 5-HT) and activating neuronal systems (mediated by other neurotransmitter systems, such as norepinephrine or dopamine (Depue & Spoont, 1986)).

Such a multineurotransmitter-based model of impulsive aggression may help to explain the apparent lack of relationship between suicidal behaviour and 5-HT function in bipolar patients in studies with fenfluramine challenge (Coccaro *et al*, 1989) or CSF 5-HIAA (Ågren, 1983; Roy-Byrne *et al*, 1983; Berrettini *et al*, 1986). Is it possible that differences exist among subject populations (e.g. bipolar versus nonbipolar) in the functioning of neuronal systems involved in the expression of impulsive aggressive behaviour? Indices of pre-synaptic noradrenergic function are reduced in bipolar patients (see Siever, 1987, for review). Hence, this deficit could impair the neuronal systems involved in activation so that neither inwardly nor outwardly directed aggression could occur. A report of non-aggressive behaviour in rats with low 5-HT levels and an accompanying noradrenergic system deficit offers some experimental support for this hypothesis (Hodge & Butcher, 1975).

A similar explanation may be given in unipolar depressed patients where an inverse relationship has been observed between prolactin responses to fenfluramine and history of suicide attempt but not with impulsive aggression (Coccaro *et al*, 1989). As reduced post-synaptic alpha$_2$ noradrenergic receptor sensitivity has been noted in depressed patients (Siever, 1987), it is possible that diminished post-synaptic noradrenergic receptor sensitivity may generally buffer the behavioural activation-inhibition system, blunting stimulus-linked activation except in times of great distress (e.g. during a severe major depressive episode). During such an episode, the individual may act upon his or her impulse against the source of distress (e.g. the worthless and/or guilt-ridden self) and attempt suicide. Despite reduced post-synaptic noradrenergic receptor sensitivity in depressed patients, evidence of noradrenergic dysregulation with wide fluctuations of pre-synaptic output has been described in depressed (particularly unipolar) patients (Siever, 1987), providing support for this hypothesis.

Clinical psychopharmacology of impulsive aggression

Psychopharmacologic agents generally used in the treatment of impulsive aggression include lithium carbonate, the non-selective beta-adrenergic antagonists, neuroleptics, and carbamazepine. Unfortunately, while these agents are often prescribed, there is limited data from double-blind clinical studies to support their use in the treatment of impulsive aggression. The best available data from double-blind, placebo-controlled studies support the use of lithium carbonate in the therapy of impulsive aggression in antisocial adults (e.g. prison inmates; Sheard *et al*, 1976), conduct-disordered adolescents (Campbell *et al*, 1984), and mentally handicapped subjects (Worrell *et al*, 1975; Tyrer *et al*, 1984). Numerous case studies and open trials, but fewer double-blinded studies, have also suggested the efficacy of high-dose beta-adrenergic antagonists in controlling aggression (Sorgi *et al*, 1986), particularly in organically compromised individuals (Elliot, 1977; Yudofsky *et al*, 1981) or schizophrenia (Sorgi *et al*, 1986). Two placebo-controlled double-blinded studies have cited the efficacy of neuroleptic agents over placebo in the treatment of suicidal and/or impulsive aggressive behaviour in adults (Montgomery & Montgomery, 1982) and children (Campbell *et al*, 1984). In the first, depot flupenthixol was found to be effective in reducing suicide attempts in a population of patients with recurrent suicide attempts and impulsive aggressive behaviour (Montgomery & Montgomery 1982). In the second study, low-dose haloperidol was found to be efficacious (though less well tolerated than lithium) in reducing aggressivity in hospitalised conduct-disordered children (Campbell *et al*, 1984). Other placebo-controlled studies of neuroleptic treatment in personality disorder patients demonstrate modest efficacy in clinician- and self-rated hostility or belligerence with low-dose haloperidol (Soloff *et al*, 1986) or a tendency toward reduced self-rated hostility with low-dose thiothixine (Goldberg *et al*, 1986). Finally, one small double-blinded, placebo-controlled cross-over study demonstrated the efficacy of carbamazepine in reducing episodes of behavioural dyscontrol and aggression in female patients with borderline personality disorder (Cowdry & Gardner, 1988).

The pharmacologic non-specificity of these agents, however, cannot allow the testing of a 5-HT hypothesis of impulsive aggression in man. While serotonin-enhancing effects of lithium carbonate have been demonstrated (Bunney & Garland-Bunney, 1987), lithium may also diminish catecholaminergic function (Linnoila *et al*, 1983b, c). Because increased noradrenergic and/or dopaminergic system function is associated with aggressive behaviour in animals (Senault, 1970; Hodge & Butcher, 1975) and in clinical studies (Brown *et al*, 1979), it is not known if lithium's anti-aggressive effects are due to increased serotonergic function or to decreased catecholaminergic function.

The same possibility exists for the non-selective beta-blockers and for carbamazepine. In addition to blocking the activity of endogenous norepinephrine at beta-receptors, non-selective beta-blockers (e.g. propranolol, pindolol) bind to 5-HT$_1$ receptors and appear to have 5-HT$_1$ agonist properties (Hjorth & Carlsson, 1986) at dosages in the range of those used in the treatment of aggressive behaviour. This raises the possibility that 5-HT$_1$ agonist effects of the non-selective beta-blockers may contribute to the clinical efficacy of these agents. However, recent reports that lipophobic beta-blockers (which do not readily cross the blood–brain barrier; e.g. nadolol) are also efficacious in the treatment of aggression (Sorgi *et al*, 1988), suggest that these agents may not work through a central 5-HT mechanism.

Similarly, carbamazepine has been shown to have effects on both 5-HT and catecholaminergic systems. Carbamazepine has been shown to increase levels of plasma tryptophan (Pratt *et al*, 1984; which may then be taken up by brain 5-HT neurons and converted to 5-HT) and to diminish dopaminergic function in some studies (Waldmeier *et al*, 1984; Post *et al*, 1985). However, the observation that carbamazepine is inactive in animal models of aggression (Koella *et al*, 1975) thought to reflect central serotonergic mechanisms (Soubrie, 1986; Depue & Spoont, 1986) suggests that carbamazepine's anti-aggressive activity may not be due to an enhancement of central 5-HT.

The efficacy of neuroleptics in aggression would appear to be due to their antidopaminergic (at low to high doses) and sedative effects (at high doses). However, the observation that neuroleptics have moderate binding affinity for 5-HT$_2$ receptors (Ortmann *et al*, 1982), that 5-HT$_2$ receptor agonists and antagonists downregulate 5-HT$_2$ receptors (Leyson *et al*, 1986), and that increased 5-HT$_2$ receptor number may be associated with violent suicidal behaviour (Stanley & Mann, 1983; Ferrier *et al*, 1986; Mann *et* *al*, 1986) raises the possibility that neuroleptics, too, may have a serotonergic mode of action in the treatment of impulsive aggression. Observations suggesting that haloperiodol (Soloff *et al*, 1986) may be more efficacious than thiothixine (Goldberg *et al*, 1986) in this regard, and those demonstrating that haloperiodol is more potent than thiothixine at 5-HT_2 receptor binding (Ortmann *et al*, 1982), provides some support for this conjecture. Accordingly, studies comparing a neuroleptic with potent 5-HT_2 antagonistic properties (e.g. clozapine; Lee & Tang, 1984; Wilmot & Szczepanik, 1989) against one without these properties (e.g. thiothixine; Ortmann *et al*, 1982), in the treatment of impulsive aggression, would be of interest.

Presently, there are at least two 5-HT specific agents available for such clinical trials. These agents include the atypical antidepressant, fluoxetine, a potent and specific 5-HT uptake inhibitor (Stark *et al*, 1985), and the atypical anxiolytic, buspirone, which has high affinity for the 5-HT_{1a} receptor (Hoyer, 1988). These agents, and others in their class, have shown activity in animal models of aggression (Berzsenyi *et al*, 1983; Olivier *et al*, 1984; Molina *et al*, 1986; McMillen *et al*, 1988) and thus support a rationale for their use in clinical trials. There is one report of tryptophan's efficacy in the treatment of aggressive schizophrenics (Morand *et al*, 1983), though high-dose tryptophan may have effects on catecholaminergic systems as well (i.e. by competing with tyrosine, the precursor of the catecholamines, for uptake into the brain; Møller, 1980). Other 5-HT specific agents currently under development, and potentially available for similar efficacy trials, include the 5-HT specific uptake inhibitors sertraline and fluvoxamine, and the 5-HT_{1a} and 5-$HT_{1a,b}$ agonists gepirone and eltoprozine, respectively. Clinical trials with each of these agents will be necessary in order to more fully understand the clinical psychopharmacology of 5-HT agents in the treatment of suicidal and/or impulsive aggressive behaviours.

Future directions

A reduction in central 5-HT function appears to be associated with a tendency toward suicidal and impulsive aggressive behaviour in both animal and clinical studies. However, while selective 5-HT agents are becoming available for clinical trials, future investigations will need to focus on the specific neuropharmacologic nature of these central 5-HT abnormalities so that pharmacotherapy can be more rationally targeted to the treatment of impulsive aggression as it appears in clinical populations.

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Is there a Relationship between Serotonin Receptor Subtypes and Selectivity of Response in Specific Psychiatric Illnesses?

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Identification of 5-HT receptor subtypes — 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$, 5-HT$_2$ (possibly A and B), 5-HT$_3$ subtypes, and possibly 5-HT$_4$ — has encouraged the manufacture of 5-HT receptor inhibitors with greater subtype specificity. However, it appears that the receptors interact, and drugs initially thought to be specific may have multiple actions. For some conditions such as anxiety/depression, almost all receptors are implicated. Clinical studies provide clear evidence that manipulation of the 5-HT system has a role in treating depression, anxiety, obsessional illness, migraine, and eating disorders. Interactions between the various receptor subtypes make it difficult to identify specific clinical functions. The 5-HT$_{1A}$ receptors may be involved in aggression, anorexia, and hypotension. The 5-HT$_{1B}$ receptors may be involved in aggression, while the 5-HT$_{1C}$ receptors may play a role in central aversion systems and anxiety/depression. The role of the 5-HT$_{1D}$ receptors remains speculative; 5-HT$_2$ receptors appear to be involved in depression, anxiety, appetite, sleep, vasoconstriction, and hypertension. Many drugs that are effective in treating migraine are potent 5-HT$_2$ antagonists. 5-HT$_3$ antagonists at high doses are effective in treating nausea and at low doses in treating anxiety. Treatment of aggression, suicidal behaviour, addiction behaviour, memory impairment, dementia, and schizophrenia with 5-HT inhibitors requires further testing.

The most surprising feature of drugs acting on the serotonin (5-HT) system is the wide range of potential disorders and behaviour in which they are possibly effective. A decade of clinical research has established the efficacy of 5-HT uptake inhibitors in depression, where they are seen to possess a broad range of efficacy which is similar to that of the reference tricyclic antidepressants (TCAs), imipramine or amitriptyline. There appears to be little evidence of any selective action on the part of the two groups within defined depressive disorders, although there may be a differential *advantage* in alleviating the associated anxiety symptoms. There is, however, increasing evidence of selective efficacy on the part of the 5-HT uptake inhibitors in conditions regarded as separate from depression.

A selective 5-HT effect is seen in obsessive–compulsive disorder, e.g. where the strong placebo-controlled evidence of efficacy of the potent 5-HT uptake inhibitors, clomipramine (with mixed effects) and fluvoxamine (selective), is in sharp contrast to the lack of efficacy of other reference TCAs, which are without potent 5-HT uptake inhibitor properties. There is also increasing evidence of the efficacy of 5-HT uptake inhibitors in bulimia, in alcoholism and other addictive behaviours, as well as possibly in aggression and suicidal behaviour, which suggests an effect beyond that normally seen with other antidepressants. It appears, therefore, that 5-HT uptake inhibitors may have a role in the management of some forms of abnormal behaviour which are not customarily regarded as treatable illnesses.

The 5-HT uptake inhibitors were developed as a result of an emphasis in research on compounds having selective effects on the serotonergic system, and recent research into the existence of different subtypes of 5-HT receptors is a natural development of this approach. The rapid changes reported in the identification of 5-HT receptor subtypes, based on animal models (Bradley *et al*, 1986), has led to the possibility of generating a series of new drugs with greater or less selectivity for these systems. Three of these 5-HT receptor subtypes, all belonging to the G Protein receptor superfamily – the 5-HT$_{1A}$, 5-HT$_{1C}$, and 5-HT$_2$ – have now been cloned and appear to be the products of separate genes (Hartig, 1989).

The relationships of these receptor subtypes with each other and their importance for psychiatric illness are the subjects of controversy. For example, in humans, the relevance of categories of 5-HT$_1$-like receptors, with types 1A, 1B, 1C, 1D, has been disputed, and doubts have been expressed about the existence of 5-HT1B receptors in the human brain. The role of these drugs, which appear active at these receptors, is still an open question in psychiatric illness or treatment. The newer, selective 5-HT$_1$-like, 5-HT$_2$ and 5-HT$_3$ agonists and antagonists, that have recently reached the stage of clinical efficacy programmes, are being examined in an extensive range of disorders and behaviours, which include such conditions as anxiety, depression, panic, obsessional illness, migraine, aggression, dysthymia, drug-induced vomiting and schizophrenia.

In some ways, these new compounds are drugs in search of an illness and the weakness of the link between animal models for illness and psychiatric illness itself needs to be re-emphasised. Therefore, it may be helpful to review the efficacy data which are available thus far for the agonists or antagonists of 5-HT_1-like, 5-HT_2 and 5-HT_3 receptors in psychiatric illnesses. Such reports are mostly preliminary – some studies are reported in full, others only in abstract form, while much of the information has not yet been subjected to critical peer review.

Serotonin, psychiatric illness and behaviour

The significance of deficiencies of 5-HT function for psychiatric illness has of course been recognised for many years, particularly for depression since 5-HT was proposed as the neurotransmitter most closely associated with mood. Fundamental questions about the nature and classification of illnesses related to depression were raised by the finding in depressed patients of a relationship between suicidal behaviour and lowered levels of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) (van Praag *et al*, 1973; Asberg *et al*, 1976). Those findings have since been confirmed at many different centres (Montgomery & Montgomery, 1982; Lopez-Ibor *et al*, 1985; Banki & Arato, 1983). Because there was evidence that the association was stronger where the suicidal attempt had been by violent means (Traskman *et al*, 1981), a relationship with a dimension of behaviour emerged that went beyond the bounds of depressive illness.

Later studies reported an association between suicidal behaviour and low CSF 5-HIAA levels, and also between aggression and low 5-HIAA levels in individuals who fulfilled DSM–III criteria for borderline personality disorder (Brown *et al*, 1979, 1982). By definition, these patients often suffered features of affective instability, inappropriate anger or lack of control of anger, suicidal behaviour and impulsiveness. The affective instability relates to conventional depression by the presence of short-lived depressive mood states that, although mostly of moderate or severe intensity, are too brief to fulfil the DSM–III criteria for major depression (Montgomery *et al*, in press). In our studies of a series of personality disorders, almost all suffered from recurrent brief depression during which hostility, impulsiveness and suicide attempts increased. There is some suggestion that impulsivity and lack of impulse control are important in these disorders, and the association with low 5-HIAA levels is seen more clearly with hot-blooded murders than where the crime was premeditated (Linnoila *et al*, 1983). Support for the dysfunction of 5-HT in personality disorders is found in the studies of Coccaro *et al* (this issue), which investigated neuroendocrine responsivity to fenfluramine challenge.

The nature of the relationship between 5-HT and these behaviours or disorders is unclear; while animal studies have shown that 5-HT is involved in the regulation of a wide range of phenomena including pain perception, thermoregulation, eating behaviour and behaviours relating to anxiety, these models have to be tested in the clinic. Recent drug development has produced compounds which have a specific and selective serotonergic effect, thus providing better pharmacological tools for investigating whether there are selective effects for particular psychiatric disorders. The development of drugs acting specifically (or relatively specifically) on 5-HT receptor subtypes such as 5-HT_1-like, 5-HT_2 and 5-HT_3 increases the precision of these investigations so that the relevance of these subtypes for particular illnesses or behaviours can now be assessed.

5-HT Uptake inhibitors

The drugs that have been studied most thoroughly in the clinical setting are the 5-HT uptake inhibitors, and the development of relatively selective compounds makes it possible to assess the relevance of their serotonergic effects to clinical efficacy. From the consistency of the results, it is possible to be relatively confident of their efficacy in some disorders, and on the basis of open studies, to raise hypotheses about possible efficacy in others.

Depressive illness

The evidence of efficacy of the selective 5-HT uptake inhibitors in the treatment of depression is substantial and convincing. The demanding requirements which are now in operation for assessing an antidepressant drug before it can be registered in Europe have resulted in more stringent methodology in clinical trials, so that we can be more sure of the efficacy of recently introduced drugs than of earlier compounds. Of the 5-HT uptake inhibitors that have so far entered clinical trial programmes, fluvoxamine, fluoxetine, citalopram and tianeptine are currently marketed in at least one European country. Two others – zimelidine and indalpine – were marketed but subsequently withdrawn because of serious adverse drug reactions. Some of the remaining 5-HT uptake inhibitors used in clinical trial programmes that are nearing completion have shown clinical efficacy, judged on the basis of large, multicentre placebo-controlled efficacy studies. The evidence of efficacy for paroxetine, for example, is now more substantial than for many licensed antidepressants and the evidence for sertraline is also well grounded.

The results of the clinical trial programmes with these new antidepressants suggest that the 5-HT uptake inhibitors are effective in the same broad range of depressed patients as the tricyclic antidepressants. Almost all of the studies adopted the DSM–III as the defining diagnostic system, which provides a relatively broad category for depression and includes both neurotic and psychotic forms. However, the suggestion that the selective pharmacological effect of 5-HT uptake inhibitors might lead to improved efficacy relative to other antidepressants has not been confirmed: an overview of the efficacy studies leads to the conclusion that the 5-HT uptake inhibitors appear to have a similar level of efficacy to that of the reference TCAs, amitriptyline or imipramine.

The possibility of improved response in subgroups of depression characterised by a deficiency in the 5-HT system has been tested in clinical efficacy studies. These sought to determine a link between pre-treatment amine metabolite status in the CSF and response to a serotonergic or to a noradrenergic antidepressant (Montgomery *et al*, 1981*a*). The lack of correlation between these measures made it apparent that any selectivity of action was overwhelmed by a general antidepressant effect.

Certain selective effects do, however, emerge in the studies. The 5-HT uptake inhibitors are associated with a transient rise in anxiety in some patients, and there was some concern that this might compromise response, particularly in patients with agitated depression. Interestingly, the reverse may be true, since with several 5-HT uptake inhibitors, there appears to be an advantage compared with TCAs in alleviating the anxiety symptoms in depressed patients with moderate or severe degrees of anxiety (Montgomery *et al*, 1981*b*, 1983; Fabre, 1988; Montgomery, 1989).

The efficacy studies with 5-HT uptake inhibitors confirm that major depression may be treated with equal success with drugs affecting the serotonergic system, affecting the noradrenergic system, or with mixed effects; 5-HT is involved in major depression but certainly not exclusively so.

Obsessive–compulsive disorder

The selective importance of 5-HT is more firmly established in obsessive–compulsive disorder (OCD) (Murphy, this issue). The strongest evidence that this is a '5-HT disorder' has come from placebo-controlled clinical treatment studies that have consistently reported the significant advantage of clomipramine but a lack of effect with other antidepressants such as desipramine and nortriptyline. This effect appears to be directly anti-obsessional, rather than depending on an antidepressant effect, as studies have shown that excluded patients with concomitant depression (Montgomery, 1980; de Veaugh-Geiss, 1989).

The anti-obsessional effect of clomipramine was thought to be mediated by its 5-HT uptake inhibiting activity, but since this drug also affects noradrenaline, it is not the most suitable pharmacological tool for investigating the biological substrate of a psychiatric illness. The selective 5-HT uptake inhibitors provide a more appropriate test of the specific importance of 5-HT in OCD. Three double-blind placebo-controlled studies have found a significant advantage for fluvoxamine compared with placebo in the treatment of OCD (Perse *et al*, 1987; Goodman *et al*, 1989; Cottraux *et al*, 1988), and open studies with others of this class are promising.

Anxiety and panic disorder

Though there is evidence for the efficacy of 5-HT uptake inhibitors in anxiety including panic disorder, the number of such studies is surprisingly small. In panic disorder, some selective advantage is reported for fluvoxamine compared with maprotiline (den Boer, 1987) and this may suggest a relatively more important role for 5-HT in this disorder than for noradrenaline.

In a well-conducted study in panic disorder, the significant advantage for fluvoxamine compared with both ritanserin and placebo on a variety of anxiety, fear and panic measures throws doubt on the usefulness of 5-HT_2 antagonists in panic and possibly anxiety (den Boer, 1987). It is difficult to assess the importance or specificity of 5-HT in panic disorder on the basis of the treatment studies reported, firstly because it is not always clear whether the patients included were suffering from coexisting depression, and secondly because the effect on panic may have been secondary to a general antidepressant response. Further investigation is needed in panic disorder, to establish where there is selectivity for 5-HT agents.

Suicide, aggression and impulse disorders

The association between low levels of 5-HIAA in the CSF and suicide attempts in depressed patients suggests that 5-HT uptake inhibitors might have some effect on suicidal behaviour. The evidence of altered 5-HT_2 receptor binding in the brains of completed suicides (Stanley & Mann, 1983) supports this view. The evidence to date is very limited, but there are some reports of an advantage in depressed patients seen early in treatment with 5-HT uptake inhibitors in terms of reducing suicidal thoughts, compared with treatment with other antidepressants (Montgomery *et al*, 1981*b*, Jacobs & Wakelin, 1986; de Wilde *et al*, 1985; Muijen *et al*, 1988). Formal placebo-controlled studies of the efficacy of 5-HT uptake inhibitors in reducing suicide attempts are clearly needed.

A possible role for 5-HT uptake inhibitors in reducing aggression has not been properly investigated, but there are several studies of lithium in this indication. The results of placebo-controlled studies provide substantial evidence of efficacy of lithium in reducing aggressive behaviour in mental handicap (Worrall *et al*, 1975; Tyrer *et al*, 1984; Craft *et al*, 1987). These studies are interesting, since it is widely thought that the effect is mediated by the action of lithium on the 5-HT system.

The accumulating evidence of an effect of 5-HT uptake inhibitors in the treatment of bulimia nervosa, much of it as yet unpublished, is also of interest. The effect appears to be selective, as drugs lacking important serotonergic effects do not appear to be effective. One theory is that the effect on bulimia is mediated by an effect on the mechanism controlling the impulse to binge. However, there is evidence from animal studies (Garattini, this issue) that 5-HT_{1A} receptor activity is associated with increased appetite, while decreased appetite is associated with other 5-HT_1 receptor subtypes. Investigations in alcoholism which are still at an early stage suggest a similar effect of 5-HT uptake inhibitors in controlling the impulse to drink in bouts, and there is also a suggestion that they may help to reduce other addictive behaviours.

Compounds affecting specific 5-HT receptor subtypes

The complexity of the involvement of 5-HT in both central and peripheral systems augered to the discovery of a range of different receptors; as this area of research is changing rapidly, the list of receptors intimated in this paper is unlikely to be complete. This list includes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_{1D}, 5-HT_2 (possibly A and B), the different 5-HT_3 subtypes and possibly 5-HT_4. As more receptor sites are identified, it becomes clearer that drugs which were thought to be specific may have multiple actions. For example, *m*-chlorphenylpiperazine (*m*-CPP), the metabolite of trazodone, originally thought to be selective, is now reported to act at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_2 receptors as well as being equipotent at α_2 receptors and less potent at α_1, dopamine and muscarinic receptors (Hamik & Peroutka, 1989; Schoeffter & Hoyer, 1989). Similarly mianserin, apart from its other actions appears to be an antagonist for 5-HT_{1C} and 5-HT_{1D}, 5-HT_2 and 5-HT_3 receptors. There is evidence to suggest an interaction between 5-HT_2 and 5-HT_1 in that 5-HT_2 antagonists may enhance 5-HT_1 function. These interactions make it difficult to identify specific clinical functions with particular receptor subtypes, and it is indeed unlikely that particular receptor subtypes have an exclusive role in specific psychiatric illnesses.

Several of the different 5-HT receptor subtypes appear to be involved in the same illnesses, although others seem to be more specific. The 5-HT_{1A} receptors seem to be involved in anxiety/depression, appetite, thermoregulation, migraine, memory and possibly obsessional illness. The 5-HT_{1B} agonists produce hypotension, and these receptors are possibly involved in aggression and in anorexia, while the 5-HT_{1C} agonists also produce anorexia. The 5-HT_2 receptors appear to be involved in depression, anxiety, appetite, sleep, vasoconstriction and hypertension. The 5-HT_3 receptors appear to be implication in anxiety, possibly depression, suppression of vomiting and promotion of gastric emptying. There are indications that these receptors are also associated with memory impairment, migraine and schizophrenia.

From this brief resumé, it seems that for some conditions such as anxiety/depression, almost all of the receptors are implicated. If this is true, the relationship between different receptor subtypes is probably complex and not amenable to simple analysis.

The 5-HT_1-like receptors

The development of new compounds that show selectivity for varying receptor subtypes has provided useful tools for the classification of receptor functions. The 5-HT_1-like receptors present a heterogenous subclass for which there are now at least four subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} and 5-HT_{1D}. Lack of specific agonists and antagonists, however, has hindered their further characterisation.

A number of compounds affecting 5-HT_{1A} receptors are now available. Buspirone, which has received the most widespread clinical testing and is marketed for the treatment of anxiety, has effects on the dopamine system as a pre-synaptic dopamine antagonist; it is not possible, therefore, to generalise very far from results seen with this drug. Ipsapirone and gepirone appear to be more specific, but the clinical testing programme has not yet reached a stage where their efficacy can be ascertained. All three drugs are partial agonists at the post-synaptic 1A receptors. These partial agonists have been found to be positive in animal models of anxiety such as the conflict models and the social behaviour models, although not all the results are in accord. Where they have initially been tested clinically, they are apparently effective. The question of the specificity of these models and compounds for anxiety has been disputed, and activity of these partial 1A agonists has, on animal models of depression, led to testing in depression (Traber, 1989); preliminary results for buspirone and gepirone are promising (Amsterdam *et al*, 1987).

The concept of anxiety and depression as a mixed disorder is gaining ground and improved efficacy has been found with a range of antidepressants in anxiety compared with benzodiazepines. It is therefore difficult to be clear whether the effects of the partial 5-HT$_{1A}$ receptor agonists in anxiety are primary or secondary to their antidepressant actions. The response of the anxiety to these compounds is slow, and comparable to the response seen with antidepressants. Further investigation of these compounds in depression is merited.

Similarly, there is evidence from animal models such as the Porsolt swimming test, reserpine-induced hypothermia, and social behavioural tests, that modulation of 5-HT$_{1B}$ receptors may help in treating depression. The relevance to man is unclear, as there are doubts about the existence of 5-HT$_{1B}$ receptors in human brains. Compounds with mixed activity like *m*-CPP have been reported to increase anxiety and obsessional symptoms acutely in obsessive–compulsive disorder (Murphy, this issue). There are suggestions that 5-HT$_{1C}$ may have a role in the control of central aversion systems and possibly anxiety/depression (Jenck *et al*, 1989). A number of antidepressants such as clomipramine, fluoxetine, tianeptine, mianserin and minaprine interact with 5-HT$_{1D}$ receptors (Fayolle *et al*, 1988), but their role in depression will remain speculative until more selective compounds become available for testing.

5-HT$_2$ Receptors

5-HT$_2$ Receptors are found in high density in those areas of the brain associated with emotion, and it is understandable that drugs affecting these receptors should be tested in anxiety, where animal behavioural models have suggested a possible function. The 5-HT antagonist properties of well-known antidepressants such as amitriptyline and mianserin suggest a role for 5-HT antagonists in treating depression. As yet, there are no drugs selective for 5-HT$_2$ receptors with sufficient clinical trials carried out to allow confident prediction of selective clinical effect.

To date, however, no studies have been reported in clearly defined depression. The best efficacy data are for ritanserin, which has mixed effects, being both a 5-HT$_2$ antagonist and a dopamine antagonist. Ritanserin has not been investigated specifically in major depressive disorder, most of the studies having been carried out on an ill-defined group of patients reportedly suffering from dysthymia (Arriaga *et al*, 1986; Bersani *et al*, 1989). There is some evidence of efficacy in this group from placebo-controlled studies, though it is not overwhelming. Ritanserin is described as a possible treatment for anxiety and depression symptoms in dysthymia, but there is some doubt whether the patients studied were in fact suffering from this disorder, as opposed to depression. Some of them were probably suffering from major depressive illness, since their scores on the Hamilton Rating Scale at entry were sufficiently high to meet the criteria for entry to a study of moderate-to-severe depression. Dysthymia is reported in some epidemiological studies (Angst & Dobler-Mikola, 1985) to have substantial overlap with major depressive disorder and with recurrent brief depression; however, claims for efficacy in dysthymia would need careful validation in a group of patients not suffering from the other two disorders.

A further area of research with 5-HT$_2$ receptors stems from the finding that clozapine has specific therapeutic advantages in treating resistant negative symptoms of schizophrenia (Kane *et al*, 1988). Clozapine has effects on the 5-HT$_2$ system, as well as being a D2 blocker, and this suggests that 5-HT$_2$ compounds might have a role in treating schizophrenia, particularly negative symptoms. A range of new clozapine-like compounds is currently being tested in neuroleptic-treated resistant schizophrenia, as well as the effect of supplementary 5-HT$_2$ antagonists such as ritanserin.

Serotonin receptor subtypes in migraine

Some drugs that are effective in treating migraine are potent 5-HT$_2$ antagonists: both ergotamine and dihydroergotamine are effective in the treatment of acute attacks and have 5-HT$_2$-antagonist properties as well as 5-HT$_{1A}$-agonist properties. Methysergide and pizotifen, also potent 5-HT$_2$ antagonists, are effective in the prophylactic treatment of migraine. The antidepressants amitriptyline and mianserin, reported as useful in migraine, are also potent 5-HT$_2$ antagonists. There is accumulated evidence of probable efficacy of some of the 5-HT$_{1A}$ agonists in treating acute attacks of migraine, and there are also reports of the efficacy of selective 5-HT$_3$ antagonists (Fozard, 1989).

5-HT$_3$ Receptors

Drugs with 5-HT$_3$-antagonist properties have been found to be active in a number of conditions, some of them outside psychiatry. One of the interesting findings is their apparently differing actions at different dose levels, which probably reflects effects on different 5-HT$_3$ receptor subtypes, although the effect of different levels of receptor occupancy needs to be explored. This complicates the task of identifying indications for which the agents may be active as well as emphasising the importance of defining precisely the disorder being tested.

Metoclopramine, which has weak 5-HT$_3$-antagonist properties and more potent dopamine-antagonist properties, is apparently effective in treating nausea but only at high doses, where the 5-HT_3 antagonism is sufficiently pronounced. This has led to the development of a range of selective 5-HT_3 antagonists. Nausea associated with chemotherapy or whole-body radiotherapy in patients with carcinoma is often sufficiently severe to compromise treatment. The usefulness of a range of compounds with 5-HT_3-antagonist effects in reducing this vomiting is therefore of importance, but available evidence suggests that efficacy is seen only at relatively high doses.

The same range of drugs is also undergoing investigation in the treatment of anxiety. Early reports suggest that efficacy may be present. The differing dose-response relationship for nausea and anxiety is suggestive of a different mechanism, and is intriguing in view of the reports of several possible subtypes of the 5-HT_3 receptor. At this early stage of investigation, it is only possible to speculate on the possible selectivity of different receptor subtypes.

A relationship between cognition and 5-HT_3 receptors drawn from animal models has aroused interest in the possible role of drugs which alter these receptors in memory impairment and dementia. Zacopride, for example, has been reported to reduce scopolamine-induced cognitive impairment in volunteers (Smith *et al*, 1989). Similarly, reports of possible applications in addictive behaviour and migraine suggest areas for further clinical investigation. The inhibitory effects of 5-HT_3 antagonists on mesolimbic dopamine systems in the rat (Costall *et al*, 1987) suggest that they have a role in treating schizophrenia.

Conclusion

Identification of different 5-HT receptor subtypes has encouraged the manufacture of a range of candidate drugs with greater or lesser specificity of action on them. Preliminary results from recent studies suggest that these receptors have both a complex interaction and a wide range of effects on behaviour. There is now evidence that manipulation of the 5-HT system is an effective way of treating a variety of psychiatric disorders. The best evidence is found in major depression, obsessional illness and anxiety disorders, where different specific serotonergic drugs are now being used in treatment. There is also evidence of efficacy in the treatment of panic, migraine and eating disorders.

For the unequivocal assessment of efficacy, well designed and well conducted placebo-controlled studies are needed in carefully defined groups of patients. In the haste to discover the full range of conditions where 5-HT specific compounds are possibly effective, there is a tendency to accelerate this process, with the attendant risk of accepting evidence of efficacy based on studies in imprecisely defined groups of patients.

Even in well-conducted studies, the overlap between some psychiatric conditions is sometimes overlooked. This overlap, for example between panic and depression, or between dysthymia and major depression, complicates the attempt to establish selective effects, and account has to be taken of this factor in the selection of patients to investigate. A more convincing test of efficacy of an antidepressant in panic will eventually be provided by a study in patients where concomitant moderate or severe depression has been excluded, as den Boer & Westenberg (1988) have suggested in a study of fluvoxamine. This approach helps to establish if an antidepressant has specific anti-panic properties. Similarly, it seems unwise to test for efficacy in dysthymia or minor depression in patients who show evidence of major depressive symptomatology. Care in separating potentially overlapping diagnostic groups is important in studies which attempt to identify efficacy in separate areas.

Placebo-controlled trials to test efficacy are needed in order to reduce observer bias and to minimise self-fulfilling prophecies. Until such studies of adequate size are carried out and replicated, it is difficult to have confidence in the reported efficacy of 5-HT compounds in some areas such as aggression, suicidal behaviour, addiction behaviour, memory impairment, dementia and schizophrenia. Nevertheless, the range of disorders where manipulation of 5-HT is established as an effective treatment appears to be wider than was previously thought. A role for manipulating specific receptor subtypes remains more controversial, and more careful clinical testing is required before specific receptor subtypes are ascribed to specific illnesses.

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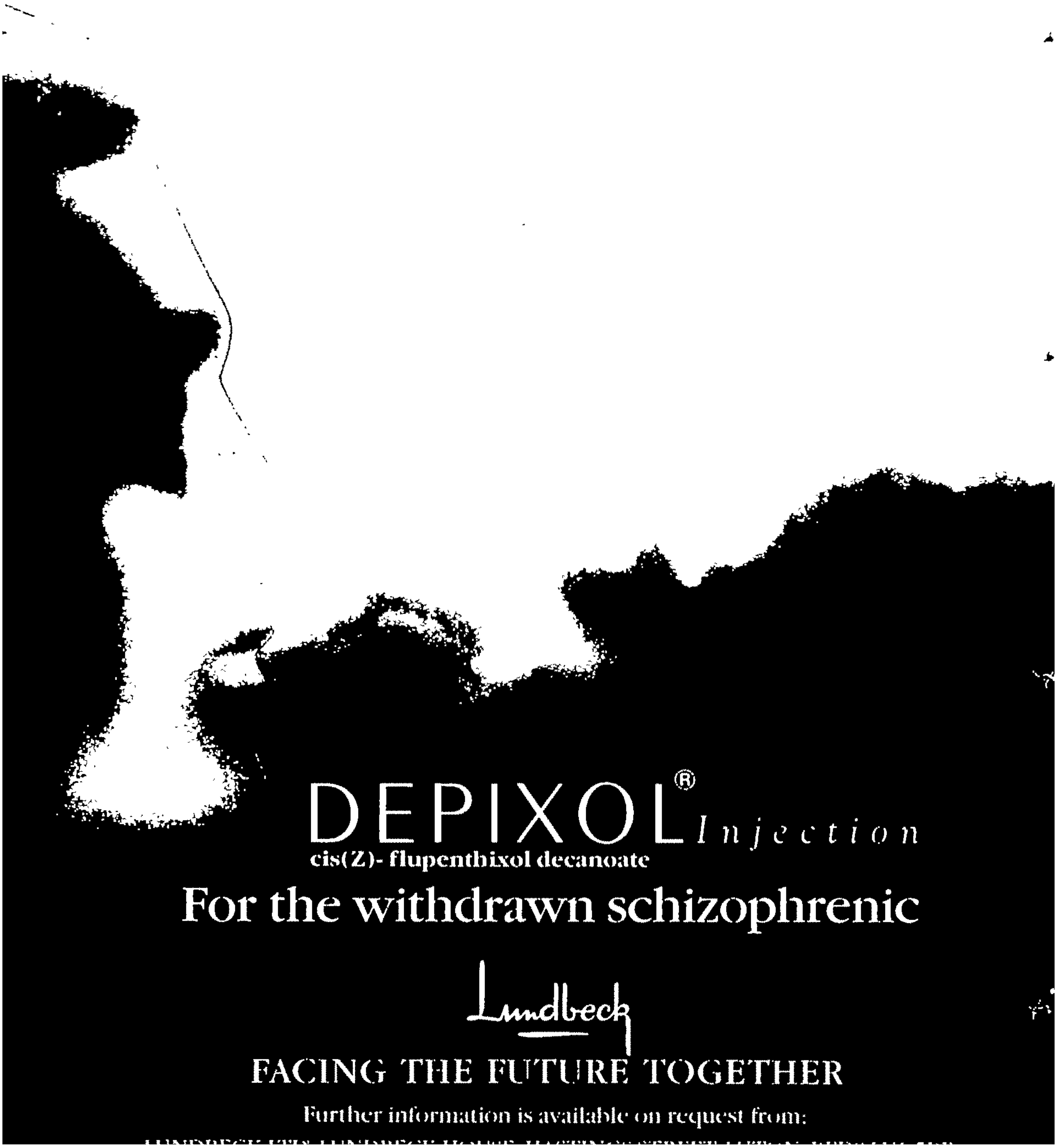

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Review Article

Psychiatric aspects of the menopause. *C. B. Ballinger* 773

Lecture

The continuum of psychosis and its genetic origins. The sixty-fifth Maudsley lecture. *T. J. Crow* 788

Papers

Insight and psychosis. *A. S. David* 798

An analysis of social competence in schizophrenia. *A. S. Bellack, R. L. Morrison, J. T. Wixted and K. T. Mueser* 809

Sex differences in the familial transmission of schizophrenia. *J. M. Goldstein, S. V. Faraone, W. J. Chen, G. S. Tolomiczencko and M. T. Tsuang* 819

Drug prescribing for schizophrenia out-patients on depot injections. Repeat surveys over 18 years. *D. A. W. Johnson and N. F. Wright* 827

Problems reported by relatives in a community study of dementia. *D. W. O'Connor, P. A. Pollitt, M. Roth, C. P. B. Brook and B. B. Reiss* 835

Sex differences in the age of onset of bipolar affective illness. *C. D. T. Sibisi* 842

An increase in violence on an acute psychiatric ward. A study of associated factors. *D. V. James, N. A. Fineberg, A. K. Shah and R. G. Priest* 846

The patients' view of life in a psychiatric hospital. A questionnaire study and associated methodological considerations. *D. H. Myers, A. Leahy, H. Shoeb and J. Ryder* 853

Puerperal insanity in the 19th and 20th centuries. *A. U. Rehman, D. St Clair and C. Platz* 861

Self-poisoning in adolescents. Hospital admissions and deaths in the Oxford region 1980–85. *C. Sellar, K. Hawton and M. J. Goldacre* 866

A structured programme for out-patient alcohol detoxification. *M. N. Collins, T. Burns, P. A. H. van den Berk and G. F. Tubman* 871

The effect of moderate weight loss on overnight melatonin secretion. *I. M. Anderson, S. E. Gartside and P. J. Cowen* 875

Point of View

Vitamin deficiency and mental symptoms. *M. W. P. Carney* 878

Brief Reports

A variant of Capgras syndrome with substitution of inanimate objects. *S. C. Rastogi* 883

Seasonal affective disorder following brain injury. *N. Hunt and T. Silverstone* 884

Manic-depressive psychosis in a mentally handicapped person. Seasonality: a clue to a diagnostic problem. *M. Arumainayagam and A. Kumar* 886

Calcium-channel blockade and depressive illness. *D. Eccleston and A. J. Cole* 889

A fatal case of water intoxication in a schizophrenic patient. *L. H. Peh, G. S. Devan and B. L. Low* 891

Symptomatic trans-sexualism. *M. Commander and C. Dean* 894

Erotomania in relation to childbirth. *D. Murray, P. Harwood and E. Eapen* 896

Anorexia nervosa and baby gazing. *J. Rutherford and G. F. M. Russell* 898

Correspondence 902

A hundred years ago. *Researched by Henry Rollin* 912

Reading About . . . Organic Psychiatry. *T. Dening* 913

Book Reviews 917

American Journal of Psychiatry, Volume 147, Number 5, May 1990 924

The Journal of Nervous and Mental Disease, Volume 178, Number 5, May 1990 *facing* 924

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Review Article

Psychiatric Aspects of the Menopause

C. B. BALLINGER

In the debates about the association between mental illness and the menopause, the psychiatric approach contradicts assertions by the gynaecological and psychoanalytic literature that the menopause has a negative effect on mental health. General population studies show that, if at all, psychiatric morbidity is more common in women in the five years before menopause. Sociocultural and family factors are more important in the aetiology of mental illness in menopausal women than physiological changes. Anxiety and depression in such women do not respond to oestrogen therapy, although some cases respond to antidepressants.

Most surveys, carried out in a variety of settings suggest that psychiatric symptoms are more common in women than men (Gove & Tudor, 1973; Dohrenwend & Dohrenwend, 1976; Gove, 1978). This finding may be partly spurious in that women admit more freely to emotional symptoms than men so increasing their scores on self-administered questionnaires (Hobbs *et al*, 1984), and women make more use of medical services, thus increasing their chances of being identified as psychiatric cases (Mechanic, 1978). However, even allowing for these methodological problems, Briscoe (1982) concluded that there is a definite excess of disorders of negative affect in women compared with men. Discussion of possible reasons for this sex difference has tended to polarise into two areas, sociological and biological, with particular emphasis on issues related to reproductive physiology such as the menstrual cycle, childbirth and the menopause.

The concept of an association between behavioural disturbance and reproductive function in women is an ancient one enshrined in the word 'hysteria', derived from the Greek word *hustera* (uterus). Veith (1965) quotes descriptions of disordered behaviour attributed to displacement of the uterus in an Egyptian papyrus from 1900 BC. In the Hippocratic writings, hysteria was considered a condition exclusive to women and related to migration of the uterus. Although the concept of hysteria is no longer applied solely to women, suggestions of an association between reproductive physiology and psychiatric disorder continue to flourish, especially with regard to premenstrual tension, post-natal depression and menopausal depression. Without doubt, it is still much more acceptable socially to have a gynaecological than a psychiatric complaint and in terms of personal responsibility for behaviour there is some attraction in the thesis that it is not 'me' but 'my hormones' that pose the problem. 'Menopause' refers to the time of cessation of menstrual periods and can therefore only be noted in retrospect. The word 'climacteric' is defined as a critical phase in life when a major change is occurring, but 'menopause' is now also used with this wider meaning and is so used in this review.

A very negative view of the menopause was promulgated as early as 1857 by Tilt, an Irish physician, who commented on "the evil effects of this time of life." He stated that nervous irritability, hysterical states and uncalled-for lowness of spirits were common at this time. Such a pessimistic view was repeated by Merson (1876) in a review of female admissions to a lunatic asylum.

Even now, many still hold negative views of the menopause, and its effect on mental illness is a focus for much debate. The gynaecological and psychiatric approaches to this subject are strikingly different, while general population studies provide more objective information on the incidence of psychiatric symptoms at the menopause. These three approaches are considered separately. Aetiology, illness behaviour and a possible treatment (hormone replacement therapy) are then also examined in this review.

The gynaecological view

Standard gynaecological textbooks still list depression, irritability, lack of confidence and poor concentration as specific symptoms of the menopause (MacNaughton, 1985; McClure-Brown, 1973; Gold & Josimovich, 1980). This negative view of mental health at the time of the menopause is not shared by all gynaecologists. Novak *et al* (1975) pointed out the dangers of attributing all symptoms in women over 40 to the menopause, while Jeffcoate (1975) stated that psychological changes were insignificant in well informed and well adjusted women but psychological symptoms arising from problems in the family and other issues were often erroneously attributed to the menopause. Previously Kupperman *et al* (1959) had a 'menopausal index' based on 11 items: vasomotor symptoms, parasthaesiae, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia and myalgia, headaches, palpitations and formication.

Some gynaecologists (e.g. Studd, 1979) continue to emphasise the presence of psychiatric symptoms in women attending menopause clinics and attribute these symptoms to the menopause and often to oestrogen deficiency. Extreme views of the impact of oestrogen deficiency on mental health had been expressed by Malleson (1953), who described menopausal depression related to oestrogen deficiency, and Wilson & Wilson (1963), whose strong feelings on this issue are reflected in the title of their paper "The fate of the non-treated post-menopausal women: a plea for the maintenance of adequate oestrogen from puberty to the grave."

The term 'menopausal syndrome' has been used extensively and includes psychiatric symptoms. An attempt made to clarify 'menopausal syndrome' was reported by Utian & Serr (1976). The symptoms most likely to be related to oestrogen deficiency were considered in two groups, an early group including hot flushes, sweats and atrophic vaginitis, and a later group including osteoporosis. Other symptoms were grouped according to aetiology under a sociocultural heading or those dependent on personality. A World Health Organization report (1981) also concluded that vasomotor symptoms and vaginal dryness were the only symptoms convincingly related to menopausal hormonal changes and stated that no relationship had been established between the hormonal changes of the menopause and psychological symptoms or changes in sexual interest.

The psychiatric view

The belief that the menopause is a time of high risk for psychiatric disorder in women is not upheld in the psychiatric literature. Indeed, there is a striking lack of comment on the menopause in psychiatric textbooks and journals. However, there has been discussion of a specific psychotic syndrome, involutional melancholia, occurring at this time of life.

The concept of involutional melancholia was introduced by Kraepelin (1906), who distinguished it from manic-depressive illness. It was said to be more common in women than in men, with onset in the 'involutional years' and symptoms of prominent agitation and hypochondriasis associated with delusions of sin, poverty and disgrace. Kraepelin (1921) later changed his mind, pointing out that the increase in new cases after the age of 45 years was just a continuation of the steady increase in new cases of affective disorder with increasing age and did not indicate the onset of a separate condition.

Although Kraepelin discarded the concept of involutional melancholia, further interest was expressed in the relationship of this condition to the menopause in women when ovarian extracts were first introduced. Werner *et al* (1934) considered involutional melancholia to be an extreme form of the menopausal syndrome caused by ovarian failure and quite separate from manic-depressive illness. They described how 20 women suffering from it were treated with ovarian extracts in the form of theelin injections for six months while 20 controls received daily injections of saline, although Wittson (1940), in a study of 23 women, reported that oestrogen therapy produced no benefit. Palmer *et al* (1941) reported negative results with stilboestrol in 11 women as did Ripley *et al* (1940) in a study of the use of oestrogen in 20 women with depressive illness attending a psychiatric clinic.

The extreme view of involutional melancholia was essentially discarded, but some authors, particularly in the United States, continued to promote it as a distinct syndrome related to the climacteric. Wittson (1940) and Malamud *et al* (1941), for example, concluded that it was a distinct clinical entity characterised by a specific symptom complex and related to problems of adjustment to involutional changes. The menopause was seen as a significant aetiological factor.

There was less enthusiasm for the concept of involutional melancholia in Britain however, and Lewis (1936) concluded that there were no clinical grounds for not classifying it as psychotic depressive illness. Kendell (1968) considered that the criteria for defining the syndrome were vague and commented on the wide age-range of subjects in some studies. In his analysis of 1080 patients with a diagnosis of either manic–depressive illness or involutional melancholia, he reported that the 55 patients who had been given the latter diagnosis could not be distinguished from the rest on diagnostic features, treatment with electroconvulsive therapy (ECT) or outcome ratings. Stenback (1963) also concluded from a detailed clinical study that there was no evidence of a specific syndrome of involutional melancholia which could be differentiated from manic–depressive illness on grounds of aetiology, symptoms, pre-morbid personality, or the course.

Weissman (1979), in a study of women with bipolar affective disorder, found that sleep disturbance, somatic preoccupation, anxiety, depression, and apathy were no more common in menopausal and post-menopausal subjects than pre-menopausal subjects. In addition, there was no indication that the menopausal and post-menopausal subjects were less likely to have had previous episodes of depression or that precipitating life stresses were a less significant factor in these groups. Weissman concluded that there was no evidence to support 'involutional melancholia'.

Two genetic studies supported Weissman's conclusion. Stenstedt (1959) studied 307 patients with a diagnosis of involutional melancholia and stated that the risk of affective disorder in parents and siblings was the same as for patients with a diagnosis of manic–depressive illness. Hopkinson (1964) compared patients who had their first attack of depressive illness before and after the age of 50 years and found them to be similar. However, he reported that agitation, which was considered to be particularly marked in involutional melancholia, was more common in the early-onset group.

Rosenthal (1968), in a detailed review of involutional melancholia, considered that there was evidence of a specific condition which may have disappeared because of the introduction of effective methods of treatment. However, the general consensus of opinion was that involutional melancholia should not be considered a separate entity and it is no longer included in the World Health Organization's *International Classification of Diseases.*

Although there may be no specific psychiatric syndrome associated with the menopause, it is possible that the physiological changes at this time may affect a woman's vulnerability to psychiatric disorder. Tait *et al* (1957) studied 54 consecutive female first admissions to mental hospital between the ages of 40 and 55 years and found no direct temporal relationship between the onset of the illness and menopause. Winokur (1973) calculated the risk of admission to hospital with an affective illness for 71 women aged 20–80 years: for the post-menopausal women there was no increased risk of being admitted within three years of the menopause.

Smith (1971) carried out a survey of 880 individuals admitted to a regional mental health centre in America and included all diagnostic groups. The occurrence of 19 life events in the year before admission, including the menarche, pregnancy and the menopause, were investigated in the patients and in 2414 controls. It was found that reaching the menopause during the previous year occurred more frequently in the controls than in the patient group.

General population surveys

The great disparity between the psychiatric and gynaecological views is presumably related to clinical practice: the psychiatrists see many women with psychiatric disorders, only a few of whom are menopausal, while the gynaecologists see many menopausal women of whom a large number present with psychiatric symptoms. In the general population surveys of menopausal symptoms it was hoped that the bias associated with clinic attendance could be avoided, giving a more balanced view of what symptoms, if any, are specifically associated with the time of the menopause.

One of the first systematic surveys of a general population sample in America was by Neugarten & Kraines (1965). A symptom check-list of 28 items was used and the symptoms were arranged in three groups: somatic, psychiatric, and psychosomatic. Four hundred and sixty women between 13 and 65 years of age were included in the survey and two symptom peaks were identified, one at puberty, when the symptoms were predominantly psychological, and one at the menopause, when the symptoms were somatic.

A survey of a British population (Dunnell & Cartwright, 1972) confirmed that there was no increase in reports of psychiatric symptoms at menopause. Complaints of 'nerves', depression, irritability and headache were more common in women under 45 years of age than women over 45 years of age, and complaints of sleeplessness, aches and pains increased steadily with age but with no peak at the time of the natural menopause. Two further British surveys, one of 269 women aged 40–60 years (Thompson *et al* 1973) and another of 638 women aged 45–54 (McKinlay & Jefferys, 1974) failed to establish any direct relationship between menopausal status and symptoms such as insomnia, fatigue and depression. However, both studies noticed a sharp increase in complaints of hot flushes and night sweats at menopause.

A detailed Dutch survey of 3000 women of 40 to 60 years-of-age (Jaszmann *et al*, 1969) also showed a sharp increase in complaints of hot flushes, from 17% in women who were still menstruating to 65% in women whose menstrual periods ceased one to two years before. Complaints of 'mental imbalance', fatigue, depression and irritability were most common in women who were still menstruating and reached a peak, although not a very marked one, in women reporting irregular menstrual periods who could be considered immediately pre-menopausal. This finding of a pre-menopausal peak in psychiatric symptoms was also noted by Bungay *et al* (1980) in a study of 1120 women aged 30–64 years. They found a peak in 'minor mental symptoms' just before the mean age at the menopause in this sample. In this survey a symptom check-list based on the menopausal index (Kupperman *et al*, 1959) was used and complaints of flushes and sweats showed a peak coinciding with the time of the natural menopause.

A study reported from Australia (Wood, 1979) showed no evidence of a significant impact of the menopause on a wide variety of symptoms. A total of 948 women from the general population between 20 and 65 years of age were assessed using a structured interview schedule. Some symptoms increased with age (e.g. sleeplessness, dizziness, weakness and joint pain) and others decreased with age (e.g. irritability and headaches) while symptoms such as depression and nervousness showed no significant trend with age. There was no evidence of any exacerbation in any of these symptoms at the time of the menopause and 64% of the post-menopausal women in the sample reported that they were free of symptoms at the time of the menopause.

None of the surveys discussed so far were carried out with a specific psychiatric interest and most used symptom check-lists based on the menopausal index (Kupperman *et al*, 1959). In 1973, Hallstrom reported the findings of a Swedish survey of 800 women in four age bands between 38 and 54 years, using standardised psychiatric interviews, and Ballinger (1975) reported a survey of 539 women between 40 and 54 years of age using the General Health Questionnaire (GHQ; Goldberg, 1972) for psychiatric screening followed by standardised psychiatric interviews. Hallstrom found no significant fluctuation in the prevalence of psychiatric illness with menopausal status but reported that women with irregular menstrual periods, who could be considered immediately pre-menopausal, had a higher frequency of mental deterioration. In Ballinger's study, the women who were still menstruating, but aged 45 to 49 years, had the highest levels of psychiatric morbidity as indicated by the GHQ, and as the mean age of the menopause in Britain is 50 years (Bungay *et al*, 1980) these women are presumably immediately pre-menopausal. This finding is consistent with those of Jaszmann *et al* (1969) and Bungay *et al* (1980) who used quite different survey techniques.

Thus the general population surveys indicate no major effect of the menopause on a variety of common psychiatric symptoms. If anything, women in the post-menopausal years show less evidence of psychiatric disturbance than younger women (Kruskemper, 1975; Weissman & Myers, 1978; Ballinger *et al*, 1985). Two areas of behaviour which do, however, seem to be influenced by the menopause are sexual behaviour and sleep.

Decreased sexual drive or loss of libido is mentioned in many lists of menopausal symptoms. The assessment of sexual drive in women presents problems in that frequency of intercourse is often determined by the sexual drive of the male partner and may bear little or no relationship to sexual interest in the female. This factor is illustrated in a report from Kinsey (1953) showing that frequency of intercourse in single women remains steady until 55 years of age and then declines, while there is a steady decline in the frequency of sexual intercourse from the 20s onwards with increasing age in married women.

It has been suggested that sexual drive in women increases at the time of the menopause (Masters & Johnson, 1966) in relation to such issues as loss of fear of pregnancy but this view has not been supported by later studies (Hallstrom, 1977; Pfeiffer *et al*, 1972; Priest & Crisp, 1972), all of which suggest a significant fall in sexual interest in women at the time of the menopause.

There are two distinct sexual problems reported by women at the time of the menopause, the first being dyspareunia, related to vaginal atrophy and vaginitis, and the second being a general reduction in sexual responsiveness which is more frequent, less clearly defined, and more complex in aetiology. Studd *et al* (1977) reported that of 300 women attending a menopause clinic only 19 complained of dyspareunia, while 58 complained of dyspareunia and loss of libido, and 59 complained of loss of libido alone.

It would appear that dyspareunia and vaginal atrophy are directly related to reduced oestrogen production in post-menopausal women and respond very well to either local or systemic oestrogen therapy (Utian, 1978; Hutton *et al*, 1978).

Reduction in sexual responsiveness is more difficult to identify and quantify than dyspareunia and it is difficult to disentangle the general effects of the ageing process from any specific effect of the menopause. Priest & Crisp (1972) reported that 25% of women in their early 40s indicated that their sexual interest had altered recently and this increased to 75% of women in their early 60s. The change over this age range was more marked in women than in men. In an American study (Pfeiffer *et al*, 1972) it was reported that 7% of women aged 46–50 years said they had no sexual interest compared with 51% of women aged 61–65. This was in marked contrast to the men in the survey, none of whom indicated no sexual interest in the 46–50-year age group and only 11% in the 61–65 age range. These two studies suggest a more significant fall in sexual interest in women over the peri-menopausal years than in men over the same age range.

A more detailed study of sexual interest was the general population sample of 800 Swedish women by Hallstrom (1977). There were enough women in the survey to be able to study the effects of increasing age and menopausal status independently, and it was found that there was a significant decline in sexual interest in the post-menopausal years independent of increasing age. Decline in sexual interest also showed a significant association with low social class, the symptom of depression, and a poor marital relationship, particularly where the husband was perceived as unsupportive. Despite the clear association between reduced sexual interest and menopausal status, Hallstrom suggests that this is an artifact related to women using the menopause as an excuse for avoiding sexual contact where there is a poor marital relationship and evidence of previous personality difficulty.

In a recent British study of 436 women aged 35–59 years, Osborn *et al* (1988) confirmed the increase in sexual dysfunction with age and its positive association with psychiatric disorder, neuroticism and marital disharmony. In contrast to Hallstrom's (1977) study there was no evidence of any significant impact of menopausal status on sexual interest, independent of age. This finding supports the view that factors such as personality, personal illness and quality of marital relationship have much more impact on sexual function in women than any physiological changes associated with the menopause.

Insomnia was included in the original menopausal index (Kupperman *et al*, 1959) and is frequently listed as part of the menopausal syndrome. As with many of the so-called menopausal symptoms, there are difficulties distinguishing between the general effects of ageing and the specific effects of the menopause. McGhie & Russell (1962) reported increasing complaints of sleep disturbance with age in a general population sample but in women the increase in complaints commenced in 'middle age' while in men there was no significant increase until after the age of 65. Jaszmann *et al* (1969) reported that 20% of pre-menopausal women complained of insomnia but this increased to 40% of women who had their last menstrual period between two and five years previously. Thompson *et al* (1973) also found complaints of insomnia more common in post-menopausal women but found that these complaints correlated with night sweats.

Ballinger (1976*a*) found that post-menopausal women indicated difficulty in getting to sleep and staying asleep more frequently than pre-menopausal women, but early-morning waking showed no significant variation with menopausal status. This variation in sleep disturbance was not merely a reflection of fluctuation in psychiatric morbidity in general (it is known that psychiatric morbidity is a factor in sleep disturbance (Orme, 1972)). The suggestion of a change in sleep pattern with menopausal status and a possible relationship of this to decreased oestrogen production in the post-menopausal years is supported by sleep laboratory studies (Thomson & Oswald, 1977*a,b*). There is, therefore, evidence to suggest that sleep pattern may be influenced by the endocrine changes of the menopause.

Aetiological factors

Although the general population surveys show no significant increase in psychiatric morbidity with the menopause, there are biological, psychoanalytic, cultural, social and family factors at this time of life which may influence mental health.

Biological factors

Most epidemiological studies of affective disorder, particularly depression, suggest that this condition is more common in women than in men. Weissman & Klerman (1977) suggest that as this difference is less apparent in old age, biological factors during the reproductive years may be pertinent. In a Scottish study of first admissions for affective disorder, Eagles & Whalley (1985) found no statistically significant increase in inception rates for depressive psychosis for women aged 45–55 years when the mean age of the menopause is 50 years. In both sexes there was a significant increase in inception rates with age, and throughout the age range, a constant excess in first admission rates for women compared with men. However, the difference in inception rates between males and females was at its maximum between 45 and 55 years and then declined after menopause. This suggests that the biological changes of menopause may have some impact on vulnerability to affective disorder, and that this cannot be simply related to oestrogen deficiency.

Endocrine studies in affective disorder have shown abnormalities in control of cortisol secretion (Sachar *et al*, 1980), response of thyroid-stimulating hormone (TSH) to thyrotropin-releasing hormone (TRH) (Calloway *et al*, 1984) and the response of growth hormone (GH) to clonidine (Mitchell *et al*, 1988). Nikula-Baumann (1971) found no significant difference between patients with a diagnosis of involutional illness and controls in urinary excretion of gonadotrophins or oestrogen, and although protein-bound iodine was lower in the patient group, the author stated that this finding was inconclusive.

In a study of hormone profiles and psychological symptoms in 85 peri-menopausal women, Ballinger *et al* (1987) showed that as well as the expected changes in reproductive hormones there were fluctuations in prolactin, cortisol, TSH and triiodothyronine with menopausal status. In post-menopausal women whose periods had ceased less than five years previously there was a marked rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels, as expected, but there was also a significant rise in TSH levels with no reduction in tri-iodothyronine, indicating a possible abnormality in the feedback mechanism at this time. Women in the early post-menopausal years with evidence of psychiatric disorder had significantly higher circulating levels of oestradiol than the other subjects with the same menopausal status. However, the significance of this finding is very doubtful in view of the rapid changes in oestrogen level at this time.

Thus the reason for an increase in psychiatric morbidity in women aged around 45–50 years is not at all clear. The main gynaecological feature at this time is the change in menstrual cycle pattern (Treloar *et al*, 1967), with both a reduction and marked variation in cycle length and frequent complaints of menorrhagia, probably due to increasing proportion of anovulatory cycles at this time (Gambrell, 1974). These changes may contribute directly to stress as well as giving very clear indications of the imminence of the menopause which, in some women, may contribute to their anxiety.

The hormonal changes of the post-menopausal years have been described in detail (Chakravarti *et al*, 1976) but there has been less emphasis on the immediately pre-menopausal hormonal changes. Sherman *et al* (1976) in a study of 10 subjects stated that the peri-menopausal women who were still menstruating had cyclical hormonal changes similar to those of younger women but with lower levels of oestrogen, higher levels of FSH, and a shorter interval from the onset of menstruation to the mid-cycle gonadotrophin peak.

Attempts have been made to correlate hormonal changes with reported symptoms. Chakravarti *et al* (1979) reported that elevated hot flush counts were associated with low levels of oestradiol in pre-menopausal women but no relationship could be established between psychiatric symptoms and endocrine measures. Ballinger *et al* (1987) found that women in the late pre-menopausal age group who were clinically depressed had significantly higher levels of TSH and tri-iodothyronine than the rest of the group, again indicating some possible abnormality of the feedback mechanism.

It is possible that the dramatic changes in feedback mechanisms in the hypothalamic pituitary axis at this time contribute to the peak in difference between male and female rates of inception of affective disorder as identified by Eagle & Whalley (1985). The fall in the difference in inception rates in the later post-menopausal years may reflect the relative stability of the hypothalamic–pituitary axis once the regular endocrine changes of the menstrual cycle cease and the upheaval of the menopausal years is over. However, it must be emphasised that even at the time of the menopause, this biological factor probably makes only a very minor contribution to the risk of developing affective disorder in women.

Psychoanalytic issues

The negative impact of the symbolic significance of the menopause on mental health in women has been greatly emphasised in early psychoanalytic literature. Deutsch (1945) saw the menopause as a time of great loss of femininity and reproductive potential. Life at this time was "pale and purposeless" and psychotherapy was difficult as there was little one could offer, "Resignation without compensation" was the only solution. Fessler (1950) also suggested that the menopause was a bad time for mental health in women because of the increased importance of penis-envy. During the time of recurrent menstruation, penis-envy was mitigated by the regular reminder of reproductive potential. However, when this was lost at the time of the menopause, women were said to return to infantile attitudes.

Loss of reproductive potential is stressed as an important issue in the psychoanalytic literature and Freud (1917) related this loss to mourning and melancholia, in keeping with the psychoanalytic view that depression was particularly common at the time of the menopause. Hoskins (1944) saw the central issue as anxiety arising from the threat to the ego of the loss of reproductive potential, a woman's "symbolic token of personal worth". Achte (1970) stressed fear of growing old and loss of femininity with its associated loss of self-esteem as important factors.

A more optimistic view of the post-menopausal years (Prados, 1967), suggested that this could be a time of stability and satisfaction. Benedek (1950) emphasised the possible advantages in the opportunity for intrapersonal reorganisation at this time. She suggested that the desexualisation of emotional needs released psychic energy for such a reorganisation but stressed the importance of personality in relation to a woman's ability to do this.

The importance of personality factors in determining how a woman will cope at the time of the menopause was also emphasised by Achte (1970). In a general population study of women aged 40–54 years (Ballinger, 1976*b*), it was found that women with evidence of psychiatric disturbance were more likely to have a past history of admission to psychiatric care, treatment with psychotropic medication or a history of attending their general practitioner with a complaint of 'nerves'. Women developing psychiatric symptoms at this time would appear to be a vulnerable group, more likely to develop psychiatric symptoms than the rest of the population at any time of life.

The most striking feature of the menopause in more recent psychoanalytic literature is its absence. Greenberg & Fischer (1983) in a critique of Freud's concepts and the female reproductive processes make no mention at all of its significance. Chessick (1988) posed 30 unresolved psychoanalytic issues in relation to feminine psychology without mention of the menopause. Professional preoccupation with the active reproductive years and lack of interest in the post-reproductive years may well influence women's attitudes and self-esteem at this time.

Cultural, social and family factors

Although much of the literature on the menopause is dominated by physiological issues there is now more interest in the social and cultural factors which may influence a woman's mental health at this time. At this time of life, a woman is likely to have to cope with major changes to her own and to family life. English (1954) emphasised the importance of these issues and suggested that improvement in education and changes in social attitudes would facilitate dealing with them. Rogers (1956) also highlighted these issues and commented on the unfortunate practice of attributing all symptoms in middle-aged women to the physiological changes of the menopause.

Culturally-determined attitudes can certainly influence how a woman copes at this time. Western culture tends to put a high value on youth, and the menopause is a clear reminder of increasing age. Mannes (1968) pointed out the difficulties of coping with reminders of ageing in a society where old age was nothing to look forward to and youth was worshipped. Negative expectations of the menopause in younger women were demonstrated by Neugarten *et al* (1968). American women in a series of age bands were asked to say what they expected would happen at the time of the menopause or, if they were post-menopausal, what symptoms they attributed to the menopause. Approximately 50% said the menopause was, or would be, troublesome, disagreeable and unpleasant but the majority of post-menopausal women indicated no major discontinuity at that time. The menopause would seem to be much worse in anticipation than in reality and this may contribute to the excess of psychiatric morbidity just before menopause.

A very different view of the menopause was described by Flint (1975, 1979) in an Indian society, where post-menopausal women experienced an increase in social standing, freedom, and self-esteem. In this group, the only symptoms reported at the time of the menopause were menstrual cycle changes.

Maoz *et al* (1970) investigated the effect of cultural differences on menopausal symptoms by comparing women of different ethnic origins who were living in the state of Israel. Oriental Arabs had the most positive attitude to the menopause and this was related to a lack of desire for any more children in a group which had large families. The women of European origin had more negative views of the menopause and factors associated with this were dissatisfaction with sexual relationships and evidence of emotional disturbance.

One of the major family changes that are likely to occur at the time of the menopause is that of children leaving home or marrying. Deykin *et al* (1966) introduced the term 'empty nest syndrome' to express the problems of adaptation. In a general population survey of women between 40 and 55 years of age, Ballinger (1975) found that women who reported that a child had married or left home in the previous year were more likely to show evidence of psychiatric disturbance. However, a somewhat different view of this issue emerges in a study of 160 women by Rubin (1979). During detailed interviews, many women expressed great relief about their children becoming independent and leaving home, especially if the offspring left in an acceptable manner such as proceeding to tertiary education.

The influence of social class on symptom frequency at the time of the menopause was investigated by Jaszmann *et al* (1969). Women who came from lower socioeconomic groups with only primary education had higher symptom levels than those from higher income groups who had gone through higher education. Severne (1979) confirmed these findings.

The issue of work in relation to adjustment at this time is discussed in Rubin's study (1979). Although many of the women interviewed felt relief about their children leaving, they expressed anxiety about their own future as individuals rather than as somebody's mother. The practical problems of returning to work, education and training were discussed, and Rubin's subjects also emphasised the importance of the quality of the marital relationship on the process of readjustment. The importance of an intimate relationship when coping with major life events has been discussed by Brown & Harris (1978) and Ballinger *et al* (1985), in a study of women between 20 and

60 years of age, found that women reporting a poor marital relationship had an increased risk of psychiatric disturbance.

The relative contribution of biological and social factors to psychiatric disturbance at this time of life were assessed by Greene & Cooke (1980) who concluded that social life events were more important. Cooke (1985) identified several relevant psychosocial variables including loss of mother before the age of 11 years, lack of full-time employment outside the home, and number of confiding relationships. However, as these studies included women between the ages of 35 and 54 years, it is difficult to ascertain how specific these factors are to problems occurring in the peri-menopausal years. A further study comparing social and biological variables investigated the prevalence of depression in a group of women aged 45–55 years (McKinlay *et al*, 1987). This concluded that the major influences on the risk of developing depression were worries about work, adolescent children, ailing husbands, and ageing parents. Menopausal status was not found to be a significant contributing factor.

When these studies are considered in conjunction with the other general population surveys, it must be concluded that social and family issues have a major impact on mental health in women at the time of the menopause as at other times of life (Brown & Harris, 1978; Ballinger *et al*, 1985). The particular issues associated with the peri-menopausal years would appear to be children becoming independent or leaving home and subsequent re-evaluation of personal role and future development.

Illness behaviour

The view that the menopause has a markedly deleterious effect on mental health as suggested by gynaecology or menopause clinic studies (Kupperman *et al*, 1959; Jones *et al*, 1977) and the early psychoanalytic writings (Deutsch, 1945; Fessler, 1950) is not upheld in the general population surveys (Neugarten & Kraines, 1965; Jaszmann *et al*, 1969; Hallstrom, 1973; Thompson *et al*, 1973; McKinlay & Jefferys, 1974; Ballinger, 1975; Wood, 1979). The views of both the gynaecologists and the psychoanalysts were based on studies of clinic attenders and these women are not representative of the general population in terms of mental health since attendance at clinics is determined by a wide variety of personal, social and cultural factors (Mechanic, 1986).

In a study of general hospital out-patient attenders Sainsbury (1960) found that the clinics with the greatest proportion of patients scoring high on the neuroticism scale were the psychiatric, general medical, gynaecological, skin and physical medicine clinics, in that order. In the gynaecology clinic sample, high neuroticism scores were associated with complaints of dysmenorrhoea, leucorrhoea, menorrhagia and sterility. Munro (1969) found 10% of 164 first-attenders at a gynaecology clinic to be 'psychiatrically unwell' and only 25% of this group had demonstrable physical illness compared with 50% of the rest. Menorrhagia was a common complaint in the 'psychiatrically unwell' group and approximately half of this group was said to be peri-menopausal.

An association between gynaecological complaints and neurotic disorders was suggested by Gregory (1957), who found that 25 of 52 patients with a diagnosis of neurosis had experienced a previous gynaecological problem compared with 2 of 46 psychotic patients. Similar findings were reported by Coppen (1965) in patients with a previous history of cervical dilatation and uterine curettage. Only 6.5% of schizophrenic patients had undergone this procedure compared with 14.6% of patients with affective disorder and 20.4% of patients with a neurotic illness.

An Australian study of women attending a gynaecology clinic (Worsley *et al*, 1977) showed that 48% of the 97 women screened using the General Health Questionnaire (GHQ) (Goldberg, 1972) obtained high scores indicating significant emotional disturbance. Complaints of menstrual dysfunction were significantly higher in the emotionally disturbed group and a definite organic diagnosis was less likely to be made than in the low-score group. Byrne (1984) also found increased rates of psychiatric disturbance in gynaecology clinic attenders compared with the general population, disorders of menstruation and pelvic pain being the most common complaints.

Ballinger (1977), using the GHQ, screened 217 women between 40 and 55 years of age who attended a gynaecology clinic for a new-patient appointment. Fifty-three per cent of the women obtained high scores compared with 29% of women in a general population sample from the same geographical area and in the same age range (Ballinger, 1975). The clinic attenders were also more likely to have had previous contact with the local psychiatric services than the general population group. Again, menorrhagia was a common symptom in this age group, and in the general population group (Ballinger, 1975) women with evidence of emotional disturbance were significantly more likely to complain of their menstrual periods being heavier than usual.

Several of these studies, therefore, suggest an association between a complaint of menorrhagia, a history of previous gynaecological investigations and psychiatric disorder. Kroger & Freed (1951) discussed possible hypotheses to account for this association but there has been little written on this topic recently. Blaikley (1949), O'Neill (1952) and Hamilton (1955) all stated that menorrhagia could be caused by emotional problems and Levy (1967) considered that this could be mediated by autonomic dysfunction in the pelvis. Little or no scientific evidence was presented to support these views. Greenberg (1983) suggested that the complaint of menorrhagia could be a manifestation of psychological disturbance on the basis of a study showing that 31 of 50 women attending a gynaecological out-patient clinic with this complaint were depressed.

Owing to the association between psychiatric disturbance and complaints of menorrhagia, it is possible that hysterectomy could be offered as an appropriate treatment. However, it has been suggested that hysterectomy precipitates psychiatric disorder. Barker (1968) reported that women who had undergone hysterectomy were subsequently more likely to be referred to a psychiatrist than controls who had had a cholecystectomy. Those women who were referred for psychiatric attention were more likely than the others to have presented originally with menorrhagia and less likely to have had significant anaemia or uterine pathology. Richards (1974) described a post-hysterectomy syndrome suggesting that hysterectomy had a considerable negative impact on mental health.

Martin *et al* (1977) described 28 of 49 women who were about to undergo hysterectomy as psychiatrically ill and suggested that some were being considered for hysterectomy for psychiatric rather than gynaecological symptoms. Ballinger (1977) found that of 29 women between 40 and 55 years who went on to undergo hysterectomy, 19 (65%) obtained high scores on the GHQ, compared with only 29% of the general population sample of women in the same age group (Ballinger, 1975). These studies suggest that high levels of psychiatric symptoms and psychiatric referral after hysterectomy are related more to the selection of patients than to hysterectomy itself. This emphasis on the importance of selection was supported by Gath *et al* (1982) in an investigation of women with benign menorrhagia for whom hysterectomy was considered appropriate treatment. Furthermore, McKinlay *et al* (1987), in a study of a cohort of 2500 women from 1981 to 1982, commented that depression may even be a cause rather than a consequence of 'surgical menopause' (stopping the menses by hysterectomy) since women undergoing this operation were less healthy and made more use of medical care than other responders before surgery.

There are various possible reasons for the association between gynaecological complaints and high levels of psychiatric morbidity. Gath *et al*'s (1982) report of the reduction in the latter after hysterectomy suggests that the stress of coping with the gynaecological complaint in itself produces significant psychiatric disturbance. However, most of the available evidence does not support this view. Sainsbury (1960) found that the mean neuroticism score for patients with chronic disabling and prognostically serious illnesses was not significantly different from that for controls, whereas the neuroticism score for attenders at a gynaecology clinic was significantly higher than that for the controls. In addition, only 32% of women attending a diabetic clinic obtained high scores on the GHQ (Wilkinson *et al*, 1987) compared with over 50% of attenders at the gynaecology clinic in the same city (Ballinger, 1977).

Benjamin *et al* (1984) suggest that 'illness behaviour' (in this case, 'consultation behaviour') could account for the observed association between physical and psychiatric ill health in some settings. Mechanic (1986) describes illness behaviour as the manner in which individuals monitor their bodies, interpret their symptoms, take remedial action, and utilise resources. This behaviour may be influenced by personality, social, and cultural factors. One personality trait considered to be of importance by Mechanic (1986) is introspection and he suggests that attention to self increases the level of reported symptoms. Tyrer *et al* (1980) found that anxious, phobic and hypochondriacal individuals were more aware of bodily sensations in terms of pulse rate than controls and this attention to self could contribute to an excess of such individuals in clinics, if it is as significant as Mechanic suggests.

Mechanic (1986) also describes how individuals in difficult social circumstances may use consultation with medical services to seek support in a socially acceptable way, as may those dealing with threatening life events (Mechanic & Volkart, 1960). Mechanic suggests that this bias would apply more to vague complaints involving symptoms and conditions that are widely distributed in the population and often untreated, such as menorrhagia and the vasomotor symptoms of the menopause. Worsley *et al* (1977) reported that family problems, particularly those with husbands and children, were common in women at the gynaecological out-patient clinic, while Byrne (1984) found that marital problems were significant in clinic attenders.

Another factor which may contribute to the excess of psychiatric morbidity in clinic attenders is direction of referral bias by the general practitioner.

Dowling & Knox (1964) commented that patients presenting with depressive illness who had experienced an unrelated physical illness in the last five years were more likely to be referred to a 'physical' clinic. Ballinger (1977) found the highest levels of psychiatric morbidity in women referred back to the gynaecological out-patient clinic after a hysterectomy.

Although most of the studies indicate that illness behaviour and referral bias are major factors in the excess of psychiatric morbidity in gynaecology clinic attenders, Jones *et al* (1977), using a 'menopause questionnaire', compared a group of women attending a menopause clinic with a group of pre-menopausal women below the age of 40 who were not attending and concluded that differences between them were related purely to menopausal status. However, no account was taken of the likely bias introduced by clinic attendance, particularly as self-referral may be operating in a menopause clinic so increasing the likelihood of bias in relation to illness behaviour. Social pressures may further increase this bias as 'women's right' to treatment for menopausal symptoms is promoted more vigorously.

Treatment

As one of the most obvious hormonal changes of the menopause is the dramatic fall in circulating oestrogen levels (Jones, 1979), there has been a great deal of emphasis on the use of oestrogen replacement therapy in management. Haspels & Van Keep (1979) suggested that the explosion of interest in the menopause in the 1960s was influenced by the development of synthetic oestrogens and the view promulgated by Wilson & Wilson (1963) that oestrogen replacement therapy would somehow guarantee eternal youth. Some authors have expressed the view that oestrogen is a more valid treatment for symptoms of anxiety and depression at the time of the menopause than psychotropic medication and emotive claims have been made, without any supporting evidence, of women being able to come off long-term psychotropic medication once they were started on oestrogen replacement therapy (Studd, 1979).

Two major issues have complicated the assessment of the effect of oestrogen on symptoms in menopausal women: one is the very large placebo effect (Coope *et al*, 1975) and the other is the use of the concept of a menopausal index or menopausal syndrome. The problems concerning the latter are illustrated in a study by Wheatley (1972). When stilboestrol was compared with opipramol in the treatment of 'menopausal symptoms', the drugs relieved overall symptom counts to the same extent. The problem of differential response had already been addressed by Sheffery *et al* (1969), in a study of the use of chlordiazepoxide, combined oestrogen and chlordiazepoxide, and oestrogen alone in women with menopausal complaints. They found that hot flushes were relieved most effectively by oestrogen or combined oestrogen and chlordiazepoxide, while combined oestrogen and chlordiazepoxide was more effective in the treatment of anxiety, vertigo and insomnia than oestrogen alone and more effective in relieving insomnia than chlordiazepoxide alone.

In a placebo-controlled trial of oestrogen therapy (Utian, 1972*a*), oestrogen was superior to placebo only on the treatment of vaginal dryness and hot flush counts and there was no significant difference between them in the relief of insomnia, irritability, depression, palpitations, backache, and reduced libido. In a further study, Utian (1972*b*) referred to a 'mental tonic' effect of oestrogen, with symptoms such as hot flushes and vaginal dryness. Campbell (1976) described a similar phenomenon as the 'domino effect'.

More detailed clinical studies of oestrogen therapy have failed to demonstrate any significant therapeutic effect of oestrogen on symptoms of depression or anxiety. In a study by George *et al* (1973), using a modified Beck inventory to rate depression, no significant difference between the effects of premarin and placebo on depression ratings was found. Thomson & Oswald (1977*a*) also failed to confirm any direct therapeutic effect of oestrogen on symptoms of anxiety or depression and Strickler *et al* (1977) failed to find any significant difference between the effect of oestrogen and placebo on a wide variety of psychological assessments in menopausal women. Despite these negative findings, there is still considerable public and media pressure for the use of oestrogens in the treatment of a wide variety of psychiatric symptoms occurring at the menopause. Dishearteningly, there is also medical opinion which supports it. Craig (1983) for example suggested that indications for oestrogen therapy should be based on a check-list of 18 items including depression and anxiety of which only two or perhaps three have been shown to respond better to oestrogen than to placebo in controlled clinical trials.

There have been several studies of the effect of psychotropic medication on symptoms in women attending menopause clinics. In a study of the use of antidepressants (Foldes, 1972) it was shown that the antidepressant was superior to placebo in the relief of depression, irritability, headache and insomnia but hot flushes were resistant to treatment. A general practice study (Wheatley, 1972) comparing the effect of stilboestrol and an antidepressant showed that depression, fatigue and vertigo were relieved more by the antidepressant while hot flushes responded better to stilboestrol. In a study of the treatment of 50 women presenting with menopausal symptoms (Kerr, 1970) all the women received oestrogen therapy to suppress the hot flush count and 25 were then treated with amitriptyline and 25 with a placebo. Amitriptyline was superior to the placebo in the treatment of depression and anxiety and also produced more improvement in insomnia, headache, palpitations and apathy.

These studies suggest that many women attending the menopause clinics have depressive illnesses responsive to antidepressant medication. This underlines the problem of attributing all symptoms presenting in women at this time of life to the hormonal changes of the menopause and in particular to low levels of circulating oestrogen. In fact, Wandless (1979) pointed out the importance of accurate diagnosis in women presenting at a menopause clinic.

A study of the treatment of sexual problems of the menopause (Studd *et al*, 1977) confirmed that dyspareunia related to vaginal atrophy responded well to oestrogen therapy. The role of hormone preparations in the management of reduced sexual response is still unclear. Bancroft (1977) in a review of hormones and sexual behaviour commented on the lack of any clear-cut correlation between hormone levels and sexual behaviour in women. Studd *et al* (1977) reported that oestrogen replacement therapy had no significant beneficial effect on loss of libido in menopausal women but combined oestradiol and testosterone implants were said to produce significant improvement. As Hallstrom (1977) has shown that sexual drive at this time is related to many factors such as psychiatric disturbance and quality of marital relationships, it is hardly surprising that there is still uncertainty about the role of physiological factors and the efficacy of hormone treatment.

There is some evidence to support the view that insomnia in women in the peri-menopausal years may respond to oestrogen therapy. Sheffery *et al* (1969) found that insomnia responded better to combined oestrogen and chlordiazepoxide than to either substance alone. In a placebo-controlled six-month cross-over study, Campbell (1976) found that oestrogen was significantly more effective than placebo in its effect on subjective complaints of insomnia. It has been suggested that insomnia at this time may be related to night sweats (Thompson *et al*, 1973) but the findings in Campbell's study suggested that the effect of oestrogen on insomnia was independent of the effect on vasomotor symptoms.

Studies of sleep disturbance in sleep laboratory conditions (Thomson & Oswald, 1977*a,b*) indicated that oestrogen was significantly superior to placebo in reducing the number of episodes of wakefulness during the night. In view of the problems arising from the use of hypnotics, it would be very reasonable to encourage the use of oestrogen preparations in women presenting with insomnia for the first time in the menopausal years, particularly if they have marked vasomotor symptoms.

There have been conflicting reports on the effects of oestrogen on memory function in menopausal and post-menopausal women. Campbell (1976) reported that oestrogen had a significant therapeutic effect on memory function. However, in this study, memory was rated by completing a self-rating for memory on an analogue rating scale, which is likely to reflect subjective concentration. Hackman & Galbraith (1977) reported a six-month pilot study of 18 patients, nine of whom received oestrogen therapy. The treated group showed a significant improvement in memory which was not found in the untreated group. Furthermore, in a three-year study of post-menopausal women between the ages of 60 and 91 years, Kantor *et al* (1973) reported that there was a steady fall on scores in memory testing, but the rate of fall was lower in the oestrogen-treated group. However, in contrast to these findings, a study of women who had undergone bilateral oophorectomy (Rauramo *et al*, 1975) found no evidence of change in memory function or cognitive functions on objective testing and no significant difference between an oestrogen treated group and an untreated group following surgery.

In conclusion, depression and anxiety in menopausal women do not respond to oestrogen replacement therapy but some women respond well to antidepressants. Oestrogen is a specific treatment for dyspareunia associated with vaginal atrophy but has no clear role in the management of general reduction in sexual drive. There is some evidence to support the view that insomnia in menopausal and post-menopausal women may respond to oestrogen but the evidence for a beneficial effect of oestrogen on memory function remains unconvincing. Strickler *et al* (1977) point out that the greatest benefit of a menopause clinic may come not from any specific hormonal or drug treatment but from the interest and support of the staff.

Conclusion

Contrary to the popular belief "It's your age, my dear", the physiological changes of the menopause have little impact on mental health. If anything, there is a fall in the prevalence of minor psychiatric disorder in the decade following the menopause. The concept of a psychotic disorder specific to the involutional years has been abandoned. There is, however, a suggestion of a peak in the excess of females over males in the onset of first attacks of affective disorder in the peri-menopausal years. Several community surveys suggest a minor peak in the prevalence of psychiatric disorder in the five years immediately before menopause. There is no evidence so far of any direct relationship between changes in reproductive hormones and psychiatric morbidity at this time but changes in thyroid function and hypothalamic feedback mechanisms may be relevant.

Events such as changes in family structure, problems with parents, involvement in outside work and reappraisal of future role have more impact on mental health at this time than the physiological changes of the menopause. Moreover, negative expectations of the menopause and the conviction that it presages a marked deterioration in mental health persist in Western culture. It is a tribute to the power of culturally-determined attitudes, media pressure and the promotion of oestrogen sales that this menopause myth persists, despite all the evidence to the contrary.

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Lecture

The Continuum of Psychosis and Its Genetic Origins

The Sixty-fifth Maudsley Lecture

T. J. CROW

Attempts to draw a line of genetic demarcation between schizophrenic and affective illnesses have failed. It must be assumed that these diseases are genetically related. A post-mortem study has demonstrated that enlargement of the temporal horn of the lateral ventricle in schizophrenia but not in Alzheimer-type dementia is selective to the left side of the brain. This suggests that the gene for psychosis is the 'cerebral dominance gene', the factor that determines the asymmetrical development of the human brain. That the psychosis gene is located in the pseudoautosomal region of the sex chromosomes is consistent with observations that sibling pairs with schizophrenia are more often than would be expected of the same sex and share alleles of a polymorphic marker at the short-arm telomeres of the X and Y chromosomes above chance expectation. That the cerebral dominance gene also is pseudoautosomal is suggested by the pattern of verbal and performance deficits associated with sex-chromosome aneuploidies. The psychoses may thus represent aberrations of a late evolutionary development underlying the recent and rapid increase in brain weight in the transition from *Australopithecus* through *Homo habilis* and *Homo erectus* to *Homo sapiens*.

Elimination of erroneous concepts

My overall theme is that scientific advance depends upon the elimination, but also upon the generation, of erroneous concepts. What we should require of our concepts is that they be formulated with sufficient clarity that the predictions they generate can be tested and found wanting. When this happens, we advance. To this end I shall draw attention to two concepts implicit in the work of Emil Kraepelin, upon whom so much of our thinking about the psychoses depends, that seem to me to be errors. These concepts have been with us for 80 years. In turn I shall generate further predictions, and shall make these as precise and testable as I can. In this way I hope to make this Maudsley lecture the first that can be shown to be completely in error within one year. When this happens you may take it that I will be disappointed. But you will enjoy it. And it will be progress.

The two errors that I identify in the work of Kraepelin are (a) that in schizophrenia (dementia praecox) intellectual function is preserved, and (b) that schizophrenia and the affective disorders are unrelated diseases. Concerning the first, Kraepelin wrote that in dementia praecox "perception is not usually lessened" and that:

> orientation is not usually disordered . . . memory is comparatively little disordered. The patients are able when they like, to give a correct detailed account of their past life, and often know accurately to a day how long they have been in the institution. (Kraepelin, 1919, p. 18)

The most striking disconfirmation of these statements is the phenomenon of age disorientation in patients with chronic schizophrenia (Crow & Mitchell, 1975; Crow & Stevens, 1978). There is no doubt there is a substantial group of patients who have severe defects of temporal orientation of an 'organic' type (Crow, 1986*a*). These defects are not due to past physical treatments or to institutionalisation, and in some cases they can be seen to have progressed with the disease process (Buhrich *et al*, 1988). Liddle was able to show that they are part of a global loss of intellectual function (Liddle & Crow, 1984). Independent of, but possibly related to, these losses are the impairments of intellectual capacity that have been shown in some cases to precede the onset of psychosis by many years (e.g. Lane & Albee, 1964; Offord & Cross, 1971).

Documentation of these intellectual deficits was part of the background to the cascade of neuroradiological investigations of brain structure that Eve Johnstone initiated with our study using computerised tomography (CT) scans (Johnstone *et al*, 1976). The relationship between intellectual losses and brain structure in schizophrenia is still quite unclear. This may be because we do not know what the fundamental structural changes are.

The meaning of the structural brain changes

A post-mortem study significantly clarified this issue. In this study (Crow *et al*, 1989*a*) we had available the brains of patients with schizophrenia and an

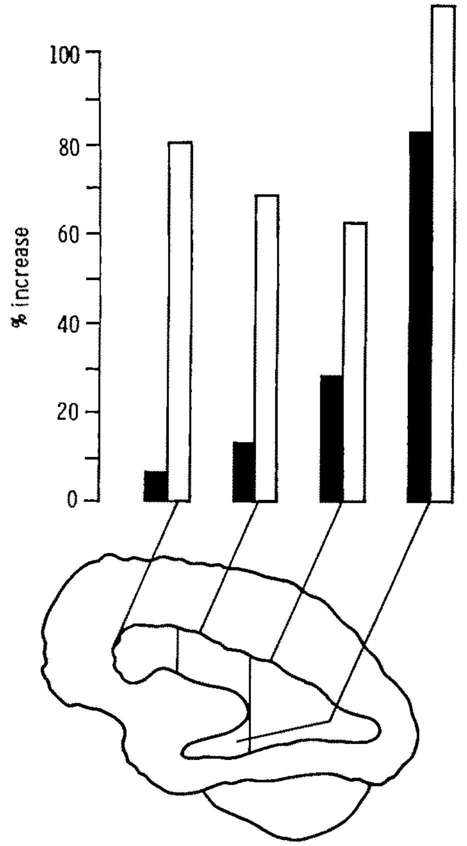

FIG. 1. Percentage increase in the components of the lateral ventricle (assessed from a radiograph following infusion of radio-opaque medium into the ventricle of one hemisphere after formalin fixation) in patients with schizophrenia (■) and with Alzheimer-type dementia (□) relative to age-matched controls. Brains with microscopically identifiable pathological change (Alzheimer-type or vascular disease) have been excluded from the schizophrenic sample. Reproduced with permission from Crow *et al* (1989*a*).

age-matched comparison group. From each brain one hemisphere (left or right at random) was taken for formalin fixation and the lateral ventricle then filled with radio-opaque material so that the extent of the ventricular system could be seen on a radiograph taken from the lateral aspect.

Figure 1 shows the percentage increase in each of the components of the lateral ventricle in patients with schizophrenia relative to the comparison group. The change is small in the anterior horn and body, but greater in the posterior and greatest in the temporal horn. This confirmed the findings of our earlier post-mortem study (Brown *et al*, 1986) – that the structural changes in schizophrenia have a degree of selectivity to the temporal lobe. The obvious interpretation is that some structure within the temporal lobe is diminished, and on present evidence the likelihood is that this is an aplasia rather than an atrophy. A possibility worth considering is that there is an arrest of development, leading to a temporal lobe that is slightly smaller and a temporal horn that is larger than normal.

In Figure 1 are also shown the increases of the components of the lateral ventricle in Alzheimer's disease relative to age-matched controls. These changes are more generalised, emphasising that there is a degree of selectivity to the temporal lobe in schizophrenia. The most striking finding, however, is that in Alzheimer's dementia the increase in area of the temporal horn is present on the left and on the right side of the brain – in schizophrenia it is present only on the left (Fig. 2). There is a significant ($P<0.001$) diagnosis-by-side interaction.

Some previous findings in schizophrenia in post-mortem studies have been lateralised. For example, Reynolds (1983) found that dopamine in the amygdala is increased relative to controls on the left but not on the right side of the brain, and we found (Brown *et al*, 1986) that the width of the parahippocampal gyrus was reduced on the left side in schizophrenia. However, what the study above (Crow *et al*, 1989*a*) allows us to do is to conclude that such asymmetry is specific to schizophrenia. This is not due to some quirk of the anatomy of the

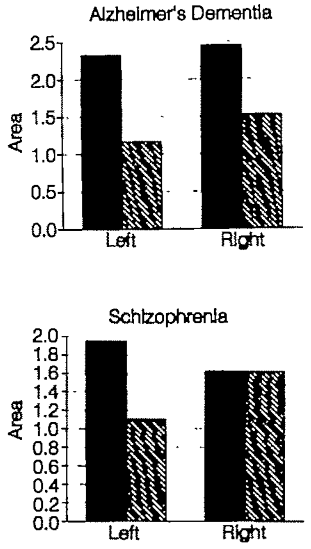

FIG. 2. Temporal horn area (assessed from the lateral aspect) in schizophrenia and Alzheimer-type dementia (■) by comparison with age-matched controls (▨). By ANOVA there is a significant diagnosis-by-side interaction ($P<0.001$). Adapted from Crow *et al* (1989*a*).

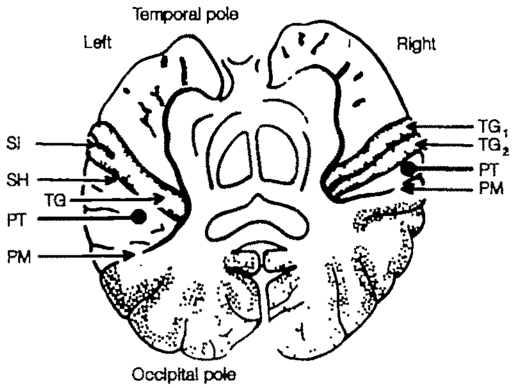

FIG. 3. Asymmetries in the human brain shown in a diagram of the superior surface of the temporal lobe as revealed by a cut extending backwards from the lateral sulcus. PT – planum temporale, of greater extent on the left; TG – transverse gyrus of Heschl, subdivided on the right; PM – posterior margin of the planum temporale; SI – sulcus intermedius of Beck; SH – sulcus of Heschl. Adapted from Geschwind & Levitsky (1968).

human brain – the change due to disease could have been symmetrical and it is not.

This takes us to a much more precise view, that the schizophrenic disease process is in some way directly related to the mechanisms that determine the asymmetries in the human brain. That there are such asymmetries has been known since the work of Dax (1865) and Broca (1861) on aphasia. In recent years their anatomical basis has been much clarified by the work of Geschwind & Levitsky (1968).

Figure 3 shows that in most people, particularly right-handed people, the lateral sulcus extends back further on the left than on the right side of the brain. This is because there are structures in the left temporal lobe, for example the planum temporale to which Geschwind & Levitsky (1968) drew attention and that forms part of the superior temporal gyrus, that are larger on the left than on the right. These of course encompass those areas of association cortex (e.g. Wernicke's area) that are responsible for speech and communication.

There must be a gene or genes that determine these developments, and these genes are among those that distinguish man from other primates. We know about the cerebral dominance gene or right-shift factor from the studies of Annett (1985), McManus (1985) and others on handedness. It is transmitted as an autosomal dominant gene, although its location is unknown. Some 30 000 genes are said to be expressed in the brain. Of these the cerebral dominance gene is surely the best candidate for the psychosis gene that we now have.

This is not a new idea. Crichton-Browne had been superintendent of the West Riding Asylum where he had carried out one of the very few studies there have been, and one of the most thorough, of brain weight in psychiatric disease. In 1879 (40 years before he gave the first Maudsley lecture) he had written:

> the cortical centres which are last organised, which are the most highly evolved and voluntary and which are supposed to be located on the left side of the brain, might suffer first in insanity. . . . (Crichton-Browne, 1879)

This is the first conclusion I invite you to consider, 110 years later. To give it greater precision I would change "which are the most highly evolved" to "because they are the most highly evolved". Crichton-Browne needed no particular technology to develop the idea, and we have needed little to document it, although an X-ray helped with measurement, and a computer helped with the ANOVA.

Demise of the Kraepelinian binary concept

A concept that has had greater popular appeal is Kraepelin's notion that schizophrenia and manic-depressive illness are distinct and unrelated disease entities. This has fared so well that no respectable textbook is without separate chapters on the two 'diseases' and much of the impetus behind modern operational diagnostic criteria (DSM-III and so forth) is directed at distinguishing these supposed entities with maximum reliability.

Serious doubts about the concept were first raised by Kendell & Gourlay's (1970) study of the patient population in the US–UK diagnostic investigation. They devised a discriminant function (Fig. 4) that achieved maximum separation of patients with a project diagnosis of affective disorder ($n = 146$) from those with a project diagnosis of schizophrenia ($n = 146$): items favouring affective illness – early morning waking, delusions of guilt and so forth – counting to the right; and items favouring a diagnosis of schizophrenia – Schneiderian first-rank features, affective flattening – counting to the left. The prediction of the two-entities principle of course is that there should be a bimodal distribution, with the major entities at either end and relatively few cases in the middle. The finding is that there is a peak at the mid-point, that is, schizoaffective cases are common rather than relatively rare as is required by the binary concept. Kendell & Gourlay repeated the investigation on a second sample, on this occasion obtaining a unimodal rather than a trimodal distribution. The investigation thus posed a serious challenge to the Kraepelinian viewpoint that has never been answered.

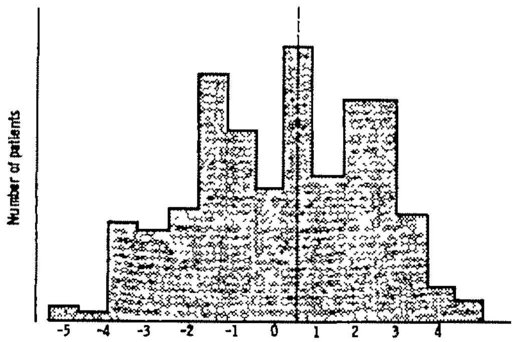

FIG. 4. The distribution of the weighted scores of 146 patients with schizophrenia and 146 with affective disorder from the US–UK study on the discriminant function derived by Kendell & Gourlay (1970) to maximise separation of the conditions.

Kraepelin himself was aware of the problem. In one of his last contributions (Kraepelin, 1920) he wrote:

> Perhaps it is also possible to tackle the difficulties which prevent us from distinguishing reliably between manic–depressive insanity and dementia praecox. No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis. . . . Nevertheless it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect.

Recent genetic evidence supports a continuum rather than two entities. For example, Angst & Scharfetter (1990*a*,*b*; and Angst *et al*, 1983) studied over 250 probands with diagnoses covering the continuum of psychotic illness as it extends from unipolar depression through bipolar affective disorder, schizoaffective illness of predominantly affective and then of predominantly schizophrenic type, to typical schizophrenia, and examined the ratio of schizophrenic to affective illnesses in the first-degree relatives (Table I).

TABLE I
Morbid risk in first-degree relatives

	UP	*BP*	*ASA*	*SSA*	*S*
No. of probands	58	31	34	35	105
No. of cases in relatives:					
schizophrenia (S)	10	4	19	18	31
affective psychoses (A)	24	6	14	4	5
S:A ratio (age-corrected)	0.30	0.47	0.92	2.99	5.05

From Angst & Scharfetter (1990*b*).
UP unipolar, BP bipolar affective disorder; ASA predominantly affective; SSA predominantly schizophrenic schizoaffective illness; S schizophrenia.

As the form of illness in the proband changes from affective to schizophrenic, the ratio of schizophrenia to affective illness in the first-degree relatives increases. There is no discontinuity such as would allow one to assert that there are two quite separate genetic components. The conclusions of Angst and his colleagues from their most recent studies (Stassen *et al*, 1988) are that:

> Typical syndrome patterns appeared in both populations [i.e. both probands and relatives]. . . . Nevertheless our analyses revealed no clear breeding true of either affective disorder or schizophrenia.

Other studies are in agreement. Thus Odegaard's (1972) investigation yielded conclusions that are almost identical to those of the Zurich group. Of great interest are the successive contributions of E. S. Gershon and colleagues at NIMH. Gershon *et al* (1982) concluded that schizoaffective psychoses were the furthest extremity of the continuum of affective disorders, and then when they started with probands with schizophrenia (Gershon *et al*, 1988) these workers found that schizoaffective illness was also genetically related to schizophrenia. The inescapable conclusion is that there is a continuum rather than two separate entities. Kraepelin was right to insist that there are prototypical affective and schizophrenic illnesses and that form of illness predicts outcome, but wrong to assert that there are two aetiologically distinct diseases. Results from the study by Maier *et al* (1989) in Mainz reinforce the continuum concept.

The conclusion has implications for the nature of the gene, as I previously suggested:

> the genes predisposing to psychosis have a degree of stability that ensures that the form of psychosis tends to remain the same within families, but there is also the possibility of change, implying that the genetic mechanisms are variable. (Crow, 1986*b*)

The genes are changing, but in small steps and in a coherent way. The only plausible model that I can see is that we have a number, perhaps a large number, of alleles at a single genetic locus.

Intergenerational changes

A potentially important aspect of this is intergenerational change in form of psychosis. Rosenthal (1970) and Penrose (1945, 1968) pointed out that the risk of schizophrenia is apparently increased in the children of parents with affective disorder.

The phenomenon was also noted by Slater (1936), Pollock & Malzberg (1940) and Powell *et al* (1973). Decina *et al* (1989) most recently looked at this question in parent–child pairs who both required admission for a psychotic illness and found that:

> while no patient with affective disorder was found amongst the children of schizophrenic parents, 50% of children of parents with affective disorder presented with schizophrenia. . . . The findings are consistent with the view that in affected families, the severity of psychopathology increases from one generation to the next and that psychotic affective disorder in the parents may predispose to schizophrenia in the children.

A related phenomenon is found in the relative risk of psychosis in the different categories of first-degree relative with both affective disorder and schizophrenia (Table II). The risk is different in the different categories of first-degree relative, being greater in children than siblings, and greater in siblings than in parents. This does not make Mendelian sense. If the gene were dominant the risk in these categories of relative would be equal; if the gene were recessive the risk to siblings would be greater than for the other two categories of relative. In the case of schizophrenia Essen-Moller (1955) offered the explanation that what is happening is that there are a number of potential parents who do not get counted because they do not have children because they suffer from schizophrenia. This is obviously true, although it is likely to be less true for affective disorder than for schizophrenia. However, it is really no more than a restatement of the problem – the survival of the schizophrenia gene in the face of a fertility disadvantage.

The phenomenon may be relevant to recent reports (e.g. from the NIMH Epidemiological Catchment Area study by Klerman *et al* (1985)) of a secular increase in affective disorder. These reports are generally based upon studies of affective disorder within families; again we see what appears to be an increase between generations.

TABLE II
Risk (per cent) of illness in different categories of first-degree relative of probands with affective disorder and schizophrenia

	Bipolar affective disorder (Price et al, *1985)*	*Schizophrenia (Zerbin-Rudin, 1972)*
Parents	4.8	6.3
Siblings	6.0	10.4
Children	9.5	13.7

From Crow (1986c).

Here we approach the central paradox of psychosis – why if these diseases are genetic in origin do they persist? Why are they so prevalent?

Book (1953) first suggested that schizophrenia was associated with a high rate of mutation, and was followed in this view by Lewis (1958) in his paper on fertility and mental illness. The suggestion may be relevant to affective disorders as well as to schizophrenia, and might relate also to changes between generations. Perhaps what we see is a high rate of change at a particular locus that has an advantage to the species in generating new variants. We might refer to this locus as the 'generator of cerebral diversity', and regard it as a characteristically human genomic feature. According to this view the recurrent psychoses are the consequence of genetic variation that has overstepped the limits of tolerable social function. Such a version of the degeneration theory is a regeneration *and* degeneration theory – a sort of steady-state theory by which new variant mutations are being frequently generated and also eliminated from the population. It views the psychoses as maladaptive variants arising from a process that is also responsible for the diversity and some of the most creative aspects of human ability.

The pseudoautosomal hypothesis

Where is the gene? The *Lancet* (1987) discussed the alternative to Kraepelin's binary viewpoint – the continuum concept of psychosis – in a sympathetic but penetrating way, emphasising the undoubted corollary that there should be a single genetic locus. Yet the *Lancet* argued that, quite apart from the various claims there have been to have established linkage for one or more of the psychoses, we have reasonable evidence that the affective disorders at least are sometimes sex linked and sometimes not. Does this not indicate that heterogeneity is already established?

My response (Crow, 1987) was that there remained one way in which homogeneity could be maintained – that the locus for psychosis should be within the pseudoautosomal region of the sex chromosomes. The pseudoautosomal region (described in more detail below) is that small region of the short arms within which there is exchange of genetic material between X and Y chromosomes in male meiosis. Thus there might be a form of sex linkage in a condition that generally follows an autosomal mode of inheritance. To maintain this view it is necessary to regard existing claims for autosomal linkage, for example to chromosome 11 (Egeland *et al*, 1987), as unfounded; this now appears more plausible (Kelsoe *et al*, 1989) than it did two years ago.

There are other reasons for taking a sex chromosomal locus for psychosis seriously. Hans Forssman gave the Blake Marsh lecture in 1970 and discussed the excess of cases of sex chromosome aneuploidy, particularly XXY and XXX, that have consistently been observed in populations of patients with psychosis. He wrote (Forssman, 1970):

> Myself I am convinced that study of aberrations of the sex chromosomes will prove to have a radical effect on large sections of psychiatric thinking. . . . That several different types of gonosomal aberration are associated with an increased risk of functional psychosis is an observation which should make us stop and think.

Heaton-Ward (1977) also emphasised the association in his Blake-Marsh lecture.

We have two alternatives. Either we suppose that the psychoses associated with sex chromosome aneuploidies represent an atypical and genetically distinct form of schizophrenia, and that the rest are, as has always been supposed, related to a gene or genes somewhere on the autosomes, or we can conjecture that the locus for psychosis is, contrary to what has generally been supposed, on the sex chromosomes. That a locus on the sex chromosomes may be combined with an autosomal pattern of inheritance comes from our recently acquired knowledge of the pseudoautosomal region. My hypothesis (Crow, 1987, 1988) is that there is a major locus for psychiatric disease within the exchange region of the X and Y chromosomes, a one-thousandth part of the human genome, and not elsewhere.

The possibility of exchange between X and Y chromosomes was first suggested by Koller & Darlington (1934), and documented in an analysis of karyotype–phenotype correlations in gonodal dysgenesis by Ferguson-Smith (1965). That it actually takes place is firmly established by molecular studies such as those of Cooke *et al* (1985), Goodfellow *et al* (1986), and Weissenbach *et al* (1987). Burgoyne (1982) introduced the term 'pseudoautosomal'. Within the pseudoautosomal region there is strict homology between genes on the X and genes on the Y chromosome, although outside this region there is substantial divergence, including at the testis-determining factor that establishes sex. Genes within the region can be transmitted from father to son as well as from father to daughter – hence the pattern of transmission is autosomal. Because there is a single obligatory cross-over in male meiosis the rate of recombination here is high relative to that elsewhere in the human genome, and there may also be a high rate of unequal recombination – a possible mechanism of generation of new mutations. The characteristic feature of pseudoautosomal transmission is same-sex concordance, that is, affected siblings will be of the same sex more often than would be expected. This arises because when the gene travels from father to child it may be carried on the X chromosome to daughters, or on the Y chromosome to sons; it could be either, but affected children are more likely to be of the same sex. The argument has been made more fully in a previous paper (Crow *et al*, 1989*b*).

Same-sex concordance in psychosis was first noted by Mott (1910). I claim Mott as the posthumous father of the pseudoautosomal hypothesis, although neither he, Penrose (1942), nor Rosenthal (1962), who later discussed concordance by sex in relation to psychiatric disease, were aware of the pseudoautosomal explanation.

Table III shows evidence for same-sex concordance in schizophrenia. It presents data dizygotic (DZ) twins from a number of studies which, because they include discordant as well as concordant pairs, have an in-built control for biased ascertainment. The DZ twin series avoid a number of the biases that Sturt & Shur (1985) drew attention to in their critique of same-sex concordance. On the whole the excess of discordant same-sex pairs is small: it does not account for the marked excess, more than 2:1, of same over mixed sex in the concordant pairs.

Summary of the evidence for the pseudoautosomal hypothesis

Firstly, as noted above, there is a same-sex concordance effect. Recently, we have presented evidence (Crow *et al*, 1989*b*) that, as predicted by the theory, this concordance is associated with paternal transmission. Our interpretation is challenged by Curtis and Gurling (1990), who have a quite different candidate for the psychosis gene – on chromosome 5, on the grounds that we have failed to take proper account of the excess of males in our series. We think

TABLE III
Concordance for schizophrenia by sex in dizygotic twin pairs

	Slater (1953)		*Rosanoff (1934)*		*Kallmann (1946)*		*Kringlen (1968)*		*Totals*	
	c.	*d.*	*c.*	*d.*	*c.*	*d.*	*c.*	*d.*	*c.*	*d.*
Same sex	11	50	10	43	34	262	6	84	61	439
Mixed sex	2	52	5	43	13	208	8	74	28	377
Same-sex : mixed-sex ratio									2.17	1.16

c. = concordant; d. = discordant.

Sign test (for the comparison with a 50 : 50 distribution): $z = 3.8$, $P < 0.0002$.

they are right that we can make further allowance for the male bias, but we disagree with them that when this correction is applied, either the same-sex concordance effect or its association with paternal transmission disappears (Crow *et al*, 1990).

However this may be, we also have molecular evidence for linkage to a pseudoautosomal probe from a study on a subset of the sibling pairs we have collected (Collinge *et al*, 1989). The telomeric probe DXYS14 is unlinked to sex and gives rise to a polymorphic series of bands on Southern blots that is suitable for an analysis of affected sibling pairs. This approach makes no assumptions about the mode of transmission, whether recessive or dominant, and does not depend upon allocating diagnoses to relatives whose status (e.g. as borderline states) may be uncertain. Sibling pairs are selected on the basis that they are both definitely affected; one then examines whether at the given locus they share alleles from the parents at or above chance expectation. If the parents have alleles *ab* and *cd* at the locus, the possibilities in the children are that they share both alleles, say *a* and *c*, from the parents, giving an IBD score of 2, that they share one allele, say *a*, giving an IBD (identity by descent) score of 1, or that they share no alleles, giving an IBD score of 0. The chance expectations of these outcomes are in the ratio of 1:2:1. In 34 pairs of siblings we find that where we would expect eight or nine sibling pairs to share two alleles, 15 have done so, and where we would expect eight or nine to share no alleles, only four have done so. This is a departure from chance expectation significant at the 1% level (Collinge *et al*, 1989). All that we have done in selecting these siblings is to ensure that both suffer from either schizophrenia or schizoaffective disorder. Such siblings will share a piece of chromosome at the psychosis locus, inherited from an affected or carrier parent. If the gene is recessive they will share the relevant part of the chromosome from both parents. However, selecting siblings for psychosis should have no influence on the distribution of alleles unless the locus in question is close (i.e linked) to the psychosis locus. We think this finding indicates that there is a linkage between schizophrenia and this genetic locus at the telomere of the short arms of the X and Y chromosomes. The result therefore supports a pseudoautosomal locus for psychosis.

If the psychoses indeed represent a continuum of variation at a single genetic locus, same-sex concordance in the affective disorders would also be expected. For bipolar illness such a finding has been reported in the NIMH Psychobiology of Depression collaborative study by Rice *et al* (1987).

TABLE IV

Chromosome and IQ abnormalities in Turner's and Klinefelter's syndromes

	Chromosomes	n	*Verbal IQ*	*Performance IQ*
Turner's syndrome	XO	35	100	88
Klinefelter's syndrome	XXY	24	83	100

Data from Netley & Rovet (1982, 1987).
In a collated sample of XXX girls a verbal-performance discrepancy similar to, but of lesser magnitude than, that in XXY males was seen (Netley, 1986).

Location of the cerebral dominance gene

I have proposed to you that psychosis is a disorder of the cerebral dominance gene, and also that the psychosis locus is in the pseudoautosomal region. It is obviously necessary for this hypothesis that the cerebral dominance gene should be located within the pseudoautosomal region, and there is evidence that this is the case (Crow, 1989). This comes from the studies of the neuropsychology of Turner's and Klinefelter's syndromes that have been conducted in Toronto by Netley & Rovet (1982, 1987).

In Turner's syndrome there is lack of an X chromosome; in Klinefelter's syndrome there is an extra X. What Netley & Rovet found was that on IQ tests they have reciprocal deficits (Table IV): in Turner's there is a performance deficit (Netley & Rovet, 1982), and in Klinefelter's a verbal deficit (Netley & Rovet,1987). The obvious interpretation is that in Turner's syndrome there is right-hemisphere dysfunction and in Klinefelter's, left-hemisphere dysfunction. Thus some factor located on the X chromosome is responsible for the relative development of the two hemispheres. However, because in normal females one X chromosome is inactivated, the abnormalities in Turner's syndrome are attributable to those parts of the X that are not inactivated. These include particularly the pseudoautosomal region. Therefore, we have an independent argument that the cerebral dominance gene is in the same part of the genome as the putative psychosis locus.

Evolutionary origins

Finally, what is the evolutionary significance of this gene?

In his book *Evolution of the Brain and Intelligence* Jerison (1973) drew attention to the relationship between brain weight and body size among primates and pointed out that in species of *Homo*, brain size has developed out of proportion to body size to a

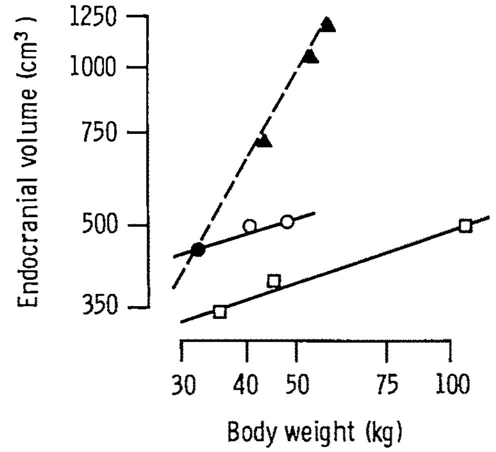

FIG. 5. Scaling of endocranial volume and body size in pongids (□ $a = 0.34$) and hominids (○ australopithecines, $a = 0.33$; ▲ *Homo* lineage, $a = 1.73$). Adapted from Pilbeam & Gould (1974).

remarkable extent. This point has been pursued by Pilbeam & Gould (1974), who consider the relationship cannot be understood in allometric terms. That is to say, the increase in size of the brain within the hominid species cannot be explained on a proportional basis (a calculation that depends upon surface area: Fig. 5). According to these authors, if the slope of the regression line is less than 0.66 the relationship between brain weight and body size can be understood as a simple increase in body size. The relationship through *Homo habilis*, *Homo erectus* to *Homo sapiens* clearly departs from this proportionality; in the hominid species there has been a substantial and significant departure from the relationships that earlier had been established. The evolution of the human brain has followed a different trajectory.

What happened to permit these developments? Jerison (1973, p. 405) has no doubt:

> We need not look far for special selection pressures toward the major enlargements of the brain within the genus *Homo*. The socialized life of a predacious primate is so obviously benefited by linguistic skills, and language is so manifestly the peculiarly human development, that change in the brain to permit that advantageous supplement to perception and communication would have had obvious selective advantages throughout the period of hominid evolution.

What allowed this to happen? Levy (1977) spelt out the benefits (and also some of the risks, and it is with one class of those risks that I think we are concerned) of having the two hemispheres perform different functions:

> Bilateralization of function arose in response to specifically human pressures, occurring in a socially organized species, the members of which were mutually interdependent. . . .

The significance of the cerebral dominance gene then is that it permitted new evolutionary developments; the significance of psychosis is that it reflects the disadvantageous spin-off of this essentially human evolutionary development. These conclusions have a bearing on the relationship between creativity and affective disorders that Jamison (1990) has discussed and also to the relationship between psychosis and achievement that Karlsson (1984) has demonstrated in the Icelandic population.

Conclusions

My conclusions are:

(a) that the psychoses represent a continuum of variation at a single genetic locus
(b) that the psychosis gene is the cerebral dominance gene
(c) that this gene is located within the pseudoautosomal region of the sex chromosomes.
(d) that the gene is a late evolutionary development, directly related to the human capacity for speech and communication.

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Insight and Psychosis

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The concept of insight into psychosis has received scant attention in the psychiatric literature. Drawing on sources such as phenomenology, clinical research and experimental psychology, it is proposed that insight is not an 'all-or-none' phenomenon but is composed of three distinct, overlapping dimensions, namely, the recognition that one has a mental illness, compliance with treatment, and the ability to relabel unusual mental events (delusions and hallucinations) as pathological. A scheme is proposed to standardise the assessment of insight to assist further research.

"Is there any knowledge in the world which is so certain that no reasonable man could doubt it?" Bertrand Russell (1912, p. 25)

In 1934, Aubrey Lewis remarked that little had been written about the concept of insight. He provided a temporary definition of the term: "a correct attitude to morbid change in oneself" (Lewis, 1934*a*), but warned that the words 'correct', 'attitude', 'morbid' and 'change' each called for discussion. Zilboorg (1952) stated that "amongst the unclarities which are of utmost clinical importance and which cause utmost confusion is the term insight". Despite or perhaps because of these assertions, contemporary authors have tended to ignore the subject. Post (1983) discards it as a concept with "limited value", and few would agree with the narrow use of insight as sole criterion upon which to distinguish neurosis from psychosis (Hamilton, 1974). Yet leading textbooks from both the United Kingdom (Gelder *et al*, 1983) and the United States (Freedman *et al*, 1975) continue to recommend the assessment of insight as an informative aspect of a patient's mental state. Some assessment of insight, explicit or implicit, and with due allowance for education and background, is crucial to the process of diagnosis, especially where psychosis is concerned. As Lewis (1934*a*, p. 343) put it: "All questions of the judgement of reality, such as . . . the consideration of insight, go to the root of the psychopathology of different conditions".

Before continuing, it is necessary to limit the area under discussion. The sudden appreciation of how parts relate to an organised whole with the accompanying "a-ha" experience is sometimes termed 'insight' by Gestalt psychologists (Harré & Lamb, 1983). This is not considered here. Nor is the term used in the popular, *Oxford English Dictionary* sense of discernment, understanding, and wisdom. The area encompassed by the term in psychoanalytic circles – usually subdivided and prefaced by 'emotional' or 'intellectual' – is so vast and treacherous that it is avoided where possible (see Zilboorg (1952) and Sandler *et al* (1973) for reviews). However, a few words in this regard are necessary for clarification. In the psychoanalytic domain, insight refers to a genuine awareness of unconscious conflicts or drives, as exemplified by Freud's (1933) dictum "where the id was there ego shall be". While not employing the term specifically, Freud realised that what present-day analysts would call insight was not merely rational self-evaluation, otherwise simply reading psychoanalytic texts would cure neurosis. Rather, it requires a much more profound appreciation of hidden truths which then lose their 'energy' (cathexis) when revealed and hence serves to bring about enduring changes within an individual (Strachey, 1934). It is clear therefore that Lewis' working definition differs from the Freudian notion. The former strives deliberately to be atheoretical and assumes that the underlying causes of the mental illness in question are unknown or perhaps unknowable, so any reference to technical constructs such as the unconscious is avoided.

This paper is restricted to an examination of insight into psychosis, using the term as it is applied in two different but related ways. The first is roughly in accord with Lewis' usage, namely, the patient's recognition that he or she is suffering from an illness and the realisation that the illness is mental. The second is the ability to relabel the experience of certain mental events as pathological. This would include realising that hearing the sound of a voice in a certain situation was in fact an auditory hallucination.

Recognition of illness

"No man is able to appreciate his own personality in any adequate way, being held within its own bounds – just as our astronomers are unable to see the shape of the galaxy in which our solar system revolves." (Mayer-Gross *et al*, 1969, p. 34)

Most normal people would concede that knowing oneself fully is an unattainable ideal. Realising that one is ill (having insight according to our definition) might therefore be held up as a considerable achievement. Jaspers (1913, p. 419) is more exacting:

> "The term 'awareness of illness' is applied to the patient's attitude when he expresses a feeling of being ill and changed, but there is no extension of this awareness to all his symptoms nor to the illness as a whole. It does not involve any objectively correct estimate of the severity of the illness nor any objectively correct judgement of its particular type. Only when this is present . . . can we speak of insight."

Here Jaspers is perhaps too stringent in distinguishing the awareness of one's mental illness from what *he* calls insight. Any awareness of this kind demands higher than normal standards of self-knowledge given the unavoidable reliance on the apparatus of mind to carry out this task, it being by definition faulty (see Ryle's (1949) discussion of 'self-knowledge'). Such a formulation must imply a "modularity of mind" (Fodor, 1983) whereby one faculty or module, in this case an observing agency, can remain functioning while another faculty is malfunctioning.

Establishing the presence of awareness may be more complicated than it appears. If it is taken to mean the "*verbalized* awareness . . . that impairment of intellectual function existed" (Eskey, 1958), then the observation that half of voluntarily admitted psychiatric patients fail to recognise their need to be in hospital (Appelbaum *et al*, 1981) needs qualification. Paradoxes of this kind, such as the conflict between non-verbal and verbal awareness, are considered again later.

Expecting any insight from a psychiatrically ill person is asking for a great deal but not the impossible. Lewis (1934*b*) in his classic study of melancholia in 61 patients found that 18 conceded illness of some kind but would not elaborate, while 14 considered that they had a mental disorder. But are the psychoses different? Again Jaspers (1913, pp. 421–422) is emphatic:

> "In psychosis there is no lasting or complete insight. . . . Sometimes at the beginning of the process we find considerable insight, the correction of delusions, the proper assessment of voices etc . . . but insight of this sort is quite transient."

The World Health Organization's (WHO, 1973) International Pilot Study of Schizophrenia in different cultures confirmed Jaspers' view. Insight was rated according to an operational definition. It was said to be present if there was some awareness of 'emotional illness' and absent if the patient vigorously denied the fact that he was disturbed. 'Lack of insight' was the most frequent symptom, occurring in 97% of the sample. The study dealt with recent-onset cases, unlike that performed by Brooks *et al* (1968), who interviewed 68 chronic schizophrenic patients of whom about one-third denied any mental illness. However, 30 spoke in terms of having 'an insanity' or 'nervous breakdown' and 16 clearly identified their illness as schizophrenia, some even naming the subtype. In a recent series of studies (McEvoy *et al*, 1989*a*,*b*), insight was measured using an open-ended questionnaire which dealt with recognition of illness plus attitudes to treatment. The average score was 8.3 (s.d. 5.9) with a possible maximum of 22, for a group of acute-on-chronic patients. The authors found that insight was independent of global psychopathology and was somewhat stable despite clinical improvement measured in other ways.

The most obvious explanation for the differing estimates of the prevalence of insight lies in the way it was assessed and, more importantly, the stage of illness of the population studied (see Heinrichs *et al*, 1985). The widely held view that insight during an acute psychosis is a contradiction in terms renders the assessment of insight in such circumstances virtually impossible.

Retrospective insight

Early psychopathologists were suspicious of patients' attitudes to their psychoses after recovery – retrospective insight. In 1823 Francis Willis asserted:

> "no man . . . can be considered sane, until he freely and voluntarily confess his delusions." (Hunter & Macalpine, 1963, p. 759)

A century later, Bleuler (1924, p. 97) wrote:

> "Even the seemingly corrected delusions in schizophrenia should rather be considered as forgotten or pushed aside."

Jaspers (1913, p. 423) was of the same opinion:

> "Patients will assert they have passed through mental illness, they are convinced of the unreality of past contents and feel quite well again but they do not talk freely about all the contents. . . . They will blush, grow pale, perspire, give evasive answers. . . . In such cases as these we cannot talk of full insight."

There is a suggestion here that Jaspers is not completely absolutist: if one cannot talk of full insight in the recovered patient, then perhaps one can talk of partial insight. Coming more up to date, Wing *et al* (1964) asked a group of 113 male schizophrenic patients just before discharge whether they would classify themselves as having been mentally ill. Twenty per cent answered yes, with a further 52% preferring terms like 'nerves' or 'strain'. Twenty three per cent said that their own delusions and hallucinations indicated that they were or had been ill. An interesting finding emerged that reveals another facet of insight, namely that 46% of the sample would regard a person who reported hearing voices as mentally ill and as many as 60% thought an average visitor would say the same. It appears then that insight into another's illness may be preserved despite the loss of personal insight (see also Brown, 1973). Cutting (1985) asked 20 remitted schizophrenics whether they thought they had had a breakdown (14 said yes) or had been ill (17 said yes) and concluded that a surprising proportion of patients do possess insight, contrary to the expectations of many psychiatrists.

Modern authors readily accept the notion that there are degrees of insight (Gelder *et al*, 1983), of which the retrospective variety is as valid as any other, and that its development is an integral part of the recovery process (Landis, 1964).

Relationship of insight to compliance

Insight is frequently assumed to predict treatment compliance. This can become misleadingly circular when the request for treatment is used as direct evidence for insight. For example, a 27-year-old man sought psychiatric treatment because he believed electricity was building up inside his brain and interfering with his thoughts. When asked why he wanted to see a psychiatrist he replied that it was because psychiatrists know about the brain and use shock therapy. The patient possessed little insight in the sense that he did not see his illness as mental despite feeling that his brain was affected in some way.

McEvoy *et al* (1981) asked 45 chronic schizophrenic patients whether they felt they were ill and required treatment. Only 13% agreed they were ill, with 27% accepting a need for medication. A systematic study of this was conducted by Lin *et al* (1979), who measured insight by asking 100 chronic schizophrenic patients three questions: do you think you (a) had to be in hospital, (b) had to see a psychiatrist, and (c) had to see a doctor? Only 31 answered yes to one of the questions and only 14 of these adhered to their medication. Of the remaining 69, 12 took their medication. Although the χ^2 test is significant at the 1% level, it should be emphasised that over half of the patients with insight did not take their medication and 17% of the ones without insight did. The same issue was examined by Van Putten *et al* (1976),who compared 29 habitual drug-refusers with 30 drug-compliers, all schizophrenics. Insight was determined using the WHO definition and it was found that 7 drug-refusers had insight compared with 18 of the drug-compliers (χ^2 was significant, $P<0.01$). Again, it is clear that insight, although related to compliance, is a rather poor predictor of it. A similar design was employed in a study of 58 schizophrenic patients, 32 of whom were non-compliant (Bartkó *et al*, 1988). These patients were generally more disturbed and tended to lack insight, that is, denied their illness.

Looking at treatment in general and not merely taking medication, Heinrichs *et al* (1985) followed 38 schizophrenic out-patients to see whether they showed "early insight" defined as "a patient's ability during the early phase of decompensation, to recognize that he or she is beginning to suffer a relapse". Twenty-four (63%) demonstrated insight and of these 22 were restabilised successfully as out-patients. In contrast, 7 of the 14 subjects without early insight, who as a group had no more symptoms, required admission to hospital.

Insight clearly aids compliance but what is peculiar about these results is that patients can have no insight into illness yet still accept and derive benefit from medication. As McEvoy *et al* (1989*a*) remark, of 52 DSM-III schizophrenics, "many subjects interviewed who consistently responded 'no' when asked if they were ill or needed treatment . . . expressed a clear willingness to take medication in the hospital." It is therefore recommended that drug compliance and awareness of illness be regarded as separate though overlapping constructs which contribute to insight.

Is insight a good thing?

Insofar as insight tends to make treatment compliance more likely it must be judged desirable. However, the value of insight may be measured in other ways. Outcome for example may be influenced by the patient's experience of illness, although Eskey (1958) and Wing *et al* (1964) found no such effect. Three-year follow-up of McEvoy *et al*'s cohort (1989*b*) showed a rather weak but enduring relationship between insight and improved prognosis.

Two studies (Soskis & Bowers, 1969; McGlashan & Carpenter, 1981) investigated the views of patients who had recovered from an acute schizophrenic episode. Both found that a negative attitude (e.g. my happiest days are in the past) or one which resulted in the illness being ignored or denied (e.g. you can never really understand your own feelings) led to poor psychosocial adjustment. Furthermore it emerged that excessive insight and an overly positive attitude bordering on 'romantic idealisation' also correlated with poor outcome. McGlashan & Carpenter concluded that the absence of a negative attitude (rather than having a positive one) is the critical factor.

Defining insight more broadly to include 'psychological mindedness', Roback & Abramowitz (1979) showed that patients with insight were better adjusted behaviourally during their hospital stay, yet they were more psychologically distressed. This concurs with the frequent observation that insight may involve a tragic and painful struggle against psychotic disturbance. That lack of insight goes along with elevated and even elated mood is supported by other workers (Van Putten *et al*, 1976; Heinrichs *et al*, 1985; Bartkó *et al*, 1988). The ubiquitous grandiose conviction that one's own mental health is intact appears to be shared by some schizophrenic individuals in whom it may reach the status of a delusion, serving perhaps a protective function, albeit temporarily. Is it possible to have too much insight – a propensity to attribute mental phenomena to the effects of illness and to seek refuge in the 'sick role', or to be subjected to continuous torturing self-examination as to whether or not one is sane? Both too much and too little could be construed as forms of abnormal illness behaviour (Pilowsky, 1978). A compromise might be sufficient insight to accept treatment but not so much that it encourages brooding on the 'reality' of how severely ill one is. This formulation has parallels in the demonstrably more favourable prognosis achieved by cancer patients who adopt a 'fighting spirit' (Greer, 1983).

I'm going mad: a special case

A person believes he is insane. The doctor agrees. The 'patient' continues:

> "You just said that I am insane. In that case my belief is not a delusion, but a correct idea. Therefore I have no delusion. Therefore I am not, after all, insane. It is only a delusion that I am insane, hence I have a delusion, hence I am insane, hence I am right, hence I am not insane. Isn't psychiatry a magnificent science?" (by Frigyes Karinthy, 1946, cited by Szasz, 1974, pp. 166–167).

The assessment of insight in a patient who believes he or she is 'going mad' is genuinely problematic although easily ridiculed, as in the above satirical piece. It does however have some basis in the real world, usually in the setting of depression, acute anxiety, or obsessional neurosis. The patient is distressed by the belief (realisation?) that his or her 'mind is going' and this dominates the presentation. The clinician avoids words like 'mad' and 'crazy' and concentrates on the form rather than the content of the preoccupation and may eventually arrive at a psychiatric diagnosis. The patient has some insight in recognising the presence of mental disorder but is in disagreement with the psychiatrist as to the correct application of terms (such as 'mad') and which elements of the disorder are fundamental to the illness category. Insight is therefore partial at best.

Pseudo-insight

Jaspers (1913) warned that listening to the patient's utterances out of context can lead to mistaken judgements about the presence of insight. This can be illustrated by the case of a 23-year-old woman who had recurrent severe episodes of bipolar affective disorder. She had received prolonged psychodynamic psychotherapy before being transferred to a unit with a strict biological treatment approach. When asked what was wrong with her she would say at times, "My main problem is my ego boundaries. They tend to fuse with my mother and that's when I get sick." On other occasions she would say, "It's a chemical imbalance that I was born with." Both statements may or may not be correct. Both contain an acknowledgement of 'morbid change' but neither can be considered insight. This is pseudo-insight: the patient merely regurgitates overheard explanations arising out of different theoretical perspectives. Someone well versed in psychological theory and jargon, who understands and uses technical terms appropriately, does not automatically possess insight. The clinician must decide whether a patient's claim that an affliction arises out of, say, an excess of neurotransmitter x, is equivalent in his or her mind to its occurrence because of an excess of radiation from Mars, a voodoo spell, or an alleged childhood misdemeanour. If so, insight is a long way off. Factual accuracy is irrelevant, otherwise the discovery of the pathogenic role of neurotransmitter y would negate the insight of someone whose understanding of mental disorder was built upon neurotransmitter x.

Insight need not imply knowledge of causality either, a view at odds with psychoanalytic formulations (Reid & Finesinger, 1952). It simply requires the acceptance of personal illness affecting the mental apparatus (the ability to think, perceive, act, remember, etc.) whose aetiology may be, and often is, unknown. Nevertheless, pseudo-insight of the kind described above may have a hermeneutic value to the patient in establishing order in the midst of chaos and may initiate a process leading to what could be called true insight.

The neuropsychology of insight

The purpose of considering neuropsychology is not to fulfil a simplistic desire to locate an 'insight centre', but rather to illuminate the mechanisms of insight into functional conditions from a knowledge of the effects of demonstrable brain lesions. A person's recognition that he or she has a mental illness is surely a specific kind of self-awareness or self-concern. The latter faculty is characteristically lost after damage to the frontal lobe (Lishman, 1987). Likewise, 'excessive self-concern' was once the prime indication for frontal leucotomy (Robinson & Freeman, 1954). However, it is the syndrome of 'anosognosia', a term coined by Babinski in 1914 meaning a lack of awareness of disease, which is of particular interest in this context (Weinstein & Kahn, 1955). This syndrome is usually confined to lesions of the right hemisphere, usually the parietal lobe (McGlynn & Schacter, 1989). The accompanying affect, especially where the lack of awareness amounts to denial, is often one of euphoria. Again, it appears that elevated mood and lack of insight go together. Denial of hemiplegia is often dramatic and bizarre, sometimes quasipsychotic. Bisiach (1988) reported a patient with left hemiplegia and hemianopia, who did not recognise his own hand even when viewed in the intact visual field. When the examiner placed the patient's left hand between his own and asked "Whose hands are these?", the patient replied blandly that all three must belong to the examiner.

Thus, the patient, lying paralysed in his hospital bed, does not see himself as ill. Similarly, the chronic schizophrenic accepts his admission to the psychiatric ward yet denies that he has a mental illness. In neither case do the denials appear to be contrived, 'psychological' defences. In the former the underlying lesion is self-evident, while in the latter there is no obvious cerebral pathology and yet it is conceivable, though highly speculative, that an undetected right hemisphere lesion might account for this too (see Cutting, 1985). Whatever the explanation, the combination of acceptance and denial of disability is further evidence of the multidimensional nature of insight, and arises again in the forthcoming discussion on delusions and hallucinations.

Relabelling mental events as pathological

> "A schizophrenic inmate of an asylum enters a country inn . . . and can only be removed by force for he expects the Queen of Holland, who wishes to marry him to arrive at any moment. He is a little ungainly creature . . . without a single advantage of mind, body or estate. It is impossible that the Queen of Holland should know anything of this poor patient in Switzerland, and if she did, he would be the last man she would wish to marry. . . . He imagines something absolutely impossible and . . . believes it to be reality. Its contradictions to reality do not exist for him." (Bleuler, 1913, p. 873)

This section deals with insight into psychotic phenomena, especially delusions, defined as a subject's ability to relabel correctly the experience of these unusual mental events as pathological. Such a consideration runs contrary to most early and some modern psychopathologists' definitions of delusions. Jaspers' position has been most influential. He stated that delusions are false judgements held with:

> "extraordinary conviction with an incomparable subjective certainty; there is an imperviousness to other experiences and to compelling counter argument; the content is impossible." (Jaspers, 1913 pp. 95–6)

Kraepelin echoed this dogma:

> "All objections that one raises to these ideas are received by the patient in a superior, incredulous manner, and glance off from his steadfast conviction without leaving the slightest impression." (Kraepelin, 1913, p. 145)

Jaspers' definition is elaborated by Mullen (1979) and concurs with the American Psychiatric Association's (1980) criteria enshrined in the third edition of the *Diagnostic and Statistical Manual* (DSM–III). According to its operational definition, delusions are:

> "sustained in spite of what almost everyone else believes and in spite of what constitutes incontrovertible and obvious proof or evidence to the contrary."

This position has been challenged recently by authors who do not accept that delusions (and hallucinations (Junginger & Frame, 1985)) are unitary concepts. In addition, and of most relevance here, they contest the notion of absolute conviction (Kendler, 1983; Garety, 1985; Brett-Jones *et al*, 1987). It is assumed that as conviction diminishes so insight increases. So-called overvalued ideas are not discussed here (see McKenna (1984) for review) nor are pseudohallucinations. The latter, according to Kräupl Taylor (1981), include by definition false perceptions plus awareness of their unreality, or in other words, the presence of insight.

Varieties of delusional experience

The Present State Examination (PSE; Wing *et al*, 1974), a semistructured psychiatric interview, requires a present/absent rating on psychotic symptoms, although it does leave room for those which are 'partial' or 'questionable'. Strauss (1969) reviewed ratings on 119 patients and found that questionable delusions and hallucinations, that is those with "intermediate levels of disbelief", accounted for over half of the sample's abnormal experiences. He proposed that psychotic phenomena are points on a continuum, a view receiving increasing support (Chapman & Chapman, 1980). Kendler (1983) and Garety & Hemsley (1987) go further and demonstrate that delusions have several independent dimensions. Kendler looked at five dimensions, including degree of conviction, bizarreness, etc., and found that no two correlated significantly. Garety & Hemsley, using visual analogue scales, rated 11 'belief characteristics' such as dismissibility, absurdity and self-evidentness, in a mixed group of deluded patients. Again the number of significant intercorrelations was small and, interestingly, 'conviction', scored highly by most subjects, did not correlate with any other single item. One conclusion is that, like the allied concept of insight, delusions are most usefully regarded as multidimensional. It should be noted that both studies used patients with schizophrenic and affective psychoses and although diagnosis did not exert a significant effect, the limited number of cases precludes definitive statements on whether or not there are qualitative differences between delusions in the two syndromes.

The degree of conviction in the deluded, as well as being unrelated to other dimensions of belief, may itself vary considerably. Sacks *et al* (1974) called this the "double-awareness phase" in the recovery from delusions, although similar intermediate states occur during their onset (Maher & Ross, 1984). These states may arise from rapid oscillations between belief and disbelief or because an individual becomes amenable to testing still firmly held beliefs against reality. This aspect was studied by Brett-Jones *et al* (1987) who found that some patients *are* influenced by evidence that disconfirms their delusions. Unfortunately, the process can work in reverse, so that chance external events are construed as confirming a (false) belief. The author argues that both normals and psychotics are most susceptible to confirmatory evidence for current beliefs (see Lord *et al*, 1979; Markovits, 1988) and that change occurs first through the acceptance of an alternative view and then the confirmation of it by experience and reasoning. Accepting the veracity of contradictory evidence for the initial belief is somewhat rarer. Nevertheless, despite the Jasperian assumption of resistance to compelling counterargument, direct confrontation of delusional beliefs with selected patients can be rewarding therapeutically (e.g. Milton *et al*, 1978; Rudden *et al*, 1982).

As well as direct evidence having a persuasive influence on certain patients' beliefs, hypothetical contradiction (Brett-Jones *et al*, 1987) may be effective in some cases (e.g. supposing the world does not come to an end when you predict it, what then?). In a pilot study of 18 psychotic day patients (David & Nestadt, in preparation), a four-point scale was used to rate strength of delusional conviction and subjects' views of the importance of medication and seeing a psychiatrist. The last two items correlated strongly with each other ($r>0.7$; $P<0.001$), but weakly with overall psychopathology, as measured by the Brief Psychiatric Rating Scale (Overall & Gorham, 1962; see also McEvoy *et al*, 1989*a*), delusional conviction, and a consensus rating by three psychiatrists of insight using the PSE definition ($r<0.5$). In addition, the utility of the question "How do you feel when people don't believe you?" was examined, a form of hypothetical contradiction. There were five possible answers ranging from poor to good insight: they're lying; I'm still sure despite what others say; I'm confused and don't know what to think; I wonder whether something's wrong with me; that's when I know I'm sick. Scores on this item correlated with the consensus insight rating significantly ($r=0.68$; $P<0.01$) but not global psychopathology ($r=0.4$). Thus, assessing relative imperviousness to another's opinion in this way appears to be a useful means of tapping insight without undue confrontation, which can be counterproductive (Milton *et al*, 1978).

Mechanisms of delusion formation

Many authors have proposed that delusions are understandable interpretations of abnormal perceptual experiences. The ability, already mentioned, of one patient to recognise false beliefs in another supports this (Brown, 1973; see Winters & Neale, 1983; Maher & Ross, 1984; Cutting 1985, for reviews). However, this does not explain the primary delusions of Jaspers nor the maintenance of abnormal beliefs in the face of contradictory evidence, implying some aetiological role for disordered thinking (see Arieti, 1974) or disordered common sense (Cutting & Murphy, 1988). There is a strong case for dissecting the logical processes leading up to the formation of beliefs both developmentally (Wellman & Bartsch, 1988) and by comparing normal and psychotic people (Hemsley & Garety, 1986). An effort has been made to do this experimentally: Huq *et al* (1988) showed that deluded subjects predicted future events more readily and on the basis of inferior standards of proof in contrast to normal and psychiatric controls. It is unlikely that all delusional experiences have a single underlying mechanism but perhaps the combination of an abnormal perception that is particularly commanding and a liability to form inferences in an idiosyncratic way, is the most parsimonious explanation for delusion formation. This is an area which deserves more research.

Epistemology

The question of how we know what we know belongs to the branch of philosophy called epistemology and is outside the scope of this article. However there have been a few attempts to discuss the psychiatric concept of insight in terms of theories of knowledge. Richfield (1954) made use of Bertrand Russell's (1912, p. 25) distinction between two kinds of knowledge: knowledge by *acquaintance* applies to "anything of which we are directly aware, without the intermediary of any process of inference or any knowledge about truths"; knowledge by *description*, on the other hand, is knowledge *about* something, knowing *that* something is true. Richfield argues that the latter type, in isolation, results in what analysts would call intellectual insight or pseudo-insight. Knowledge by acquaintance seems closer to true insight since it is the result of the actual experience of sense-data. However, as soon as abnormal experiences such as hallucinations are considered, we run into problems. For insight into a hallucination to occur, sense-data must be known both by acquaintance (the direct experience) and at the same time by description, that is, an inference must be made that the perception is false (does not arise from a real stimulus). Such epistemological gymnastics arise because few philosophers (other than Jaspers) have been sufficiently informed to tackle the issue of insight in psychosis.

Knowing and not knowing

Although some insight into psychotic phenomena is commonly accepted, it remains mysterious how contradictory beliefs can be maintained simultaneously (Bleuler, 1913). Sigmund Freud (1913, p. 142) claimed:

> "The strange behaviour of patients, in being able to combine a conscious knowing with not knowing, remains inexplicable by what is called normal psychology."

He overcame this by introducing a new psychology or metapsychology which could accommodate *unconscious* knowing. As stated in the introduction, this is awkward territory and for the present purposes, best avoided. Unfortunately, the vivid illustrations of this very paradox and the pathos they engender, described by Bleuler as autistic thinking (see quotation, p. 801), and by Sacks *et al* (1974) as "double awareness", plus everyday clinical experience, force us to attend to this baffling problem.

It is belief in the impossible, rather than the merely implausible, which constitutes the greatest challenge to causal psychological explanation. Although impossibility is inherent in Jaspers' definition of delusions, in practice some delusions are less plausible than others. Possibility is a property of the content rather than form of a delusion, an aspect which has been given scant attention in the phenomenology literature (see Winters & Neale, 1983). 'Impossible' in this context can be defined as contravening the laws of Euclidean space and time. Examples include existing in the past as well as the present (e.g. a patient who maintained he was Shakespeare, knowing that the Bard died in 1616 and that we are in the 20th century); having inside one's body something larger than oneself (e.g. a nuclear power station); being in two places at one time (e.g. a patient with reduplicative paramnesia who claimed to be in a Boston hospital and Paris simultaneously – see Weinstein & Kahn (1955)) and so on. Perhaps the most vivid examples are the nihilistic delusions of Cotard (1882). Here, the patient suffering from psychotic depression will state that he or she is dead, cannot speak, or does not exist, despite their very utterance being disconfirmation of such a state of affairs. When pressed the patient may produce an explanatory contradiction, for example "I am a living corpse". This exception to Descartes' proof of existence is explained by Jaspers (1913, p. 94) not in terms of a lack of reason but as a failure of the primary experience of 'Being', in which case lack of insight does not apply. The other cases are less easily dismissed but a similar line of argument can be invoked, namely that primary sense-data, perhaps distorted through a defective perceptual system, when of particular personal relevance, can over-ride, inhibit or coexist with knowledge gained from prior events, logic and common sense. The schizophrenic patient who felt that he had an actual power station inside him, complete with labourers, machinery, cooling towers, etc., knew it was impossible yet was sure it was so. The terror of this reality was, for him, undeniable.

Psychological mechanisms

There are models in neuropsychology which explain dual awareness such as the split brain (Sperry, 1968), where the cognitive contents of one hemisphere are unavailable to the other. Also recognition without awareness can be demonstrated in normals using priming and masking techniques (Marcel, 1983) and in some cases of agnosia. For example patients with prosopagnosia (inability to recognise faces usually due to bilateral parieto-occipital damage) may react electrophysiologically with a galvanic skin response to a familiar face yet maintain their lack of recognition despite repeated questioning (Bauer, 1984). It must be conceded that these are rather curious instances of knowledge without insight from which it is difficult to generalise.

An example of different levels of awareness with which we are all familiar occurs in relation to memory, when we recognise a name, person, or place which we have been unable to recall. These examples of systems and their contents being "informationally encapsulated" (Fodor, 1983), viewed by many as a property of the normal brain (Marcel, 1983), provide a basis for understanding delusions, and also insight in the presence of psychosis. More studies examining logical inference in deluded (Hemsley & Garety, 1986) and brain-damaged (Bisiach, 1988) subjects and mechanisms of perceptual aberration (Slade & Bentall, 1988) are required before specific explanatory models can be developed.

The conundrum of knowing and not knowing may rest on a false dichotomy. Cognitive behaviourism, which distinguishes instead between knowing and doing, has shed some light on this issue. It is recognised that therapies for phobias and obsessions that rest entirely on altering behaviour, eschewing insight, are highly effective. Modification of the underlying irrational fears and compulsions may then follow suit. Thus there can be a disjunction between thought and action (see Rachman, 1983). In addition, exposure treatment for dysmorphophobia of delusional intensity has been found to reduce delusional conviction as well as avoidance behaviour, despite the erroneous belief being unalterable by rational argument (Marks & Mishan, 1988).

It is a prerequisite of the behavioural approach that patients act against their beliefs regardless of how tenaciously they are held. Therefore, it is less surprising to find that not all deluded patients automatically act on their delusions. Indeed, Hamilton (1974) stated that deluded people are less likely to act on their beliefs than those with overvalued ideas, whose conviction is less firm and whose insight is correspondingly greater. Occasionally patients do act on their delusions, sometimes with catastrophic consequences. Although little is known about which factors determine this, some workers posit that certain kinds of delusions are particularly liable to be acted upon, but demographic variables and other elements of the mental state exert a substantial influence too (Taylor, 1985). It is not yet known in what way strength of conviction is related to delusionally motivated behaviour although research into this difficult area is in progress (Wessely, personal communication).

A novel account of schizophrenic delusions and hallucinations which combines elements of information processing and neuropsychology has been proposed by Frith (1987). He postulates that an uncoupling of thought – or a species of it, willed intention – and action, is a fundamental pathological mechanism. Put another way, the schizophrenic acts, speaks, and thinks without insight into his or her intention.

In summary, despite Freud's pessimism, there are now explanatory models in experimental psychology which can account for knowing and not knowing. If developed, these models would assist greatly in the complex task of the assessment of insight.

Conclusions

The concept of insight goes to the heart of our thinking about psychosis and has important implications for management. At present insight is assessed in a variety of *ad hoc* ways which obscure its meaning and potential. The following scheme is an attempt to clarify this by showing its main components (Fig. 1).

It is suggested that insight has at least three dimensions: (a) awareness of illness, (b) the capacity to relabel psychotic experiences as abnormal, and (c) treatment compliance. An attempt at standardising the assessment is made which relates to each facet of insight (Appendix). More research of a clinical phenomenological kind is needed in order to validate this scheme and to determine the true place of this neglected area in the understanding of mental disorders. Current models in cognitive and neuropsychology may be usefully applied to uncover underlying mechanisms. Finally it is hoped that as clinicians rediscover the concept of insight they will feel more inclined to encourage patients to rediscover it too, allowing them to play a more active role in recovery. As one patient eloquently described it:

> "When I get worked up, I often experience a slight recurrence of delusional thoughts . . . I might start testing some theory. Let me see whether that car turns the corner behind me. . . . Then it must be following me! . . . This kind of thinking is dangerous. I can [now] control my mind sufficiently to prevent such thoughts getting out of control and destroying my inner self." (First person account cited by Wing (1975))

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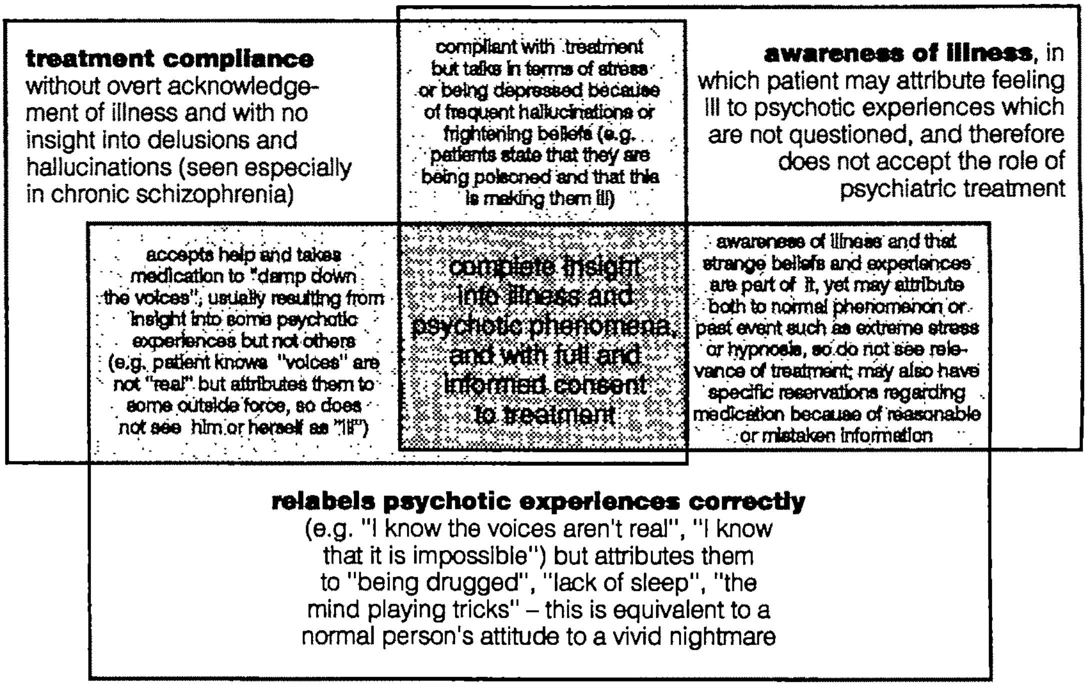
treatment compliance without overt acknowledgement of illness and with no insight into delusions and hallucinations (seen especially in chronic schizophrenia)
compliant with treatment but talks in terms of stress or being depressed because of frequent hallucinations or frightening beliefs (e.g. patients state that they are being poisoned and that this is making them ill)
awareness of illness, in which patient may attribute feeling ill to psychotic experiences which are not questioned, and therefore does not accept the role of psychiatric treatment
accepts help and takes medication to "damp down the voices"; usually resulting from insight into some psychotic experiences but not others (e.g. patient knows "voices" are not "real" but attributes them to some outside force, so does not see him or herself as "ill")
complete insight into illness and psychotic phenomena, and with full and informed consent to treatment
awareness of illness and that strange beliefs and experiences are part of it, yet may attribute both to normal phenomenon or past event such as extreme stress or hypnosis, so do not see relevance of treatment; may also have specific reservations regarding medication because of reasonable or mistaken information
relabels psychotic experiences correctly (e.g. "I know the voices aren't real", "I know that it is impossible") but attributes them to "being drugged", "lack of sleep", "the mind playing tricks" – this is equivalent to a normal person's attitude to a vivid nightmare

FIG. 1 Diagram showing main components of insight.

Appendix

Schedule for assessing the three components of insight

1a. Does patient accept (includes passive acceptance) treatment (medication and/or admission and/or other physical and psychological therapies)?

Often = 2 (may rarely question need for treatment)
Sometimes = 1 (may occasionally question need for treatment)
Never = 0 (ask why)

If 1 or 2, proceed to:

1b. Does patient ask for treatment unprompted?

Often = 2 (excludes inappropriate requests for medication etc.)
Sometimes = 1 (rate here if forgetfulness/disorganisation leads to occasional requests only)
Never = 0 (accepts treatment after prompting)

2a. Ask patient: "Do you think you have an illness?" or "Do you think there is something wrong with you?" (mental, physical, unspecified)

Often = 2 (thought present most of the day, most days)
Sometimes = 1 (thought present occasionally)
Never = 0 (ask why doctors/others think he/she does)

If 1 or 2 proceed to:

2b. Ask patient: "Do you think you have a mental/psychiatric illness?"

Often = 2 (thought present most of the day, most days)
Sometimes = 1 (thought present occasionally, minimum once per day)
Never = 0

If 1 or 2 proceed to:

2c. Ask patient: "How do you explain your illness?"

Reasonable account given based on plausible mechanisms (appropriate given patient's social, cultural and educational background, e.g. excess stress, chemical imbalance, family history, etc.) = 2
Confused account given, repetition of overheard explanation without adequate understanding or "don't know" = 1
Delusional explanation = 0

3a. Ask patient: "Do you think the belief that . . . [insert specific delusion] is *not* really true/happening?" or "Do you think that . . . [insert specific hallucination] is *not* really there/happening?"

Often = 2 (thought present most of the day, most days)
Sometimes = 1 (thought present occasionally, minimum once per day)
Never = 0

If 1 or 2 proceed to:

3b. Ask patient: "How do you explain these phenomena [the belief that . . . hearing that voice/seeing that image, etc.]?"

Part of my illness = 2
Reaction to outside event/s (e.g. 'tiredness', 'stress', etc) = 1
Attributed to outside forces (may be delusional) = 0

Maximum score = 14.

Supplementary question (hypothetical contradiction)

"How do you feel when people don't believe you [when you talk about . . . (delusion or hallucinatory experience)]?"

They're lying = 0
I'm still sure despite what others say = 1
I'm confused and don't know what to think = 2
I wonder whether something's wrong with me = 3
That's when I know I'm sick = 4.

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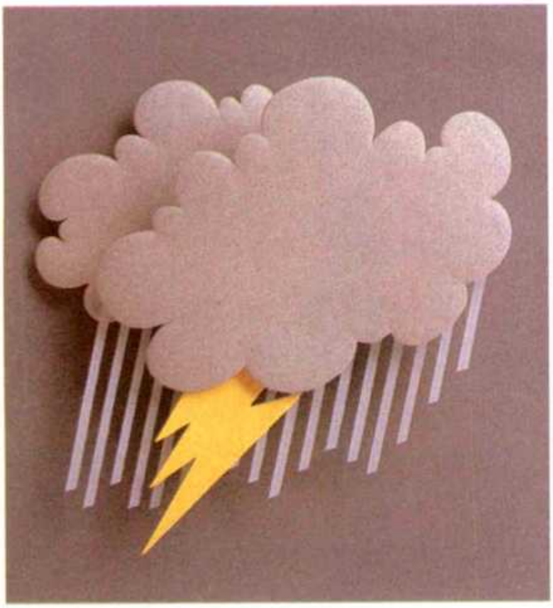
Prothiaden

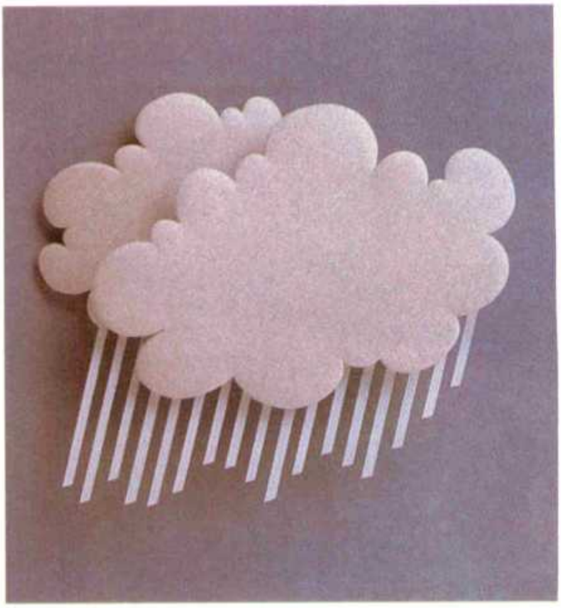
Dothiepin Hydrochloride B.P.

BOOTS PHARMACEUTICALS

TOMORROW'S STANDARD TODAY

PRESCRIBING INFORMATION Presentation: Prothiaden is Dothiepin Hydrochloride B.P. an antidepressant of the tricyclic group. It is available as 25mg capsules and 75mg tablets. **Uses:** Prothiaden is indicated in the treatment of depression and associated anxiety. **Dosage:** Prothiaden should be given in a dosage of 75 to 150mg daily, based on response and severity. This may be taken as a single evening dose. In certain circumstances, i.e. in hospital use, Prothiaden has been given in dosages up to 225mg daily. Elderly – half the normal dose may be sufficient. **Precautions and Contra-indications:** Prothiaden has anticholinergic properties, therefore, it may precipitate urinary retention in susceptible individuals and its use should be avoided in patients with existing or potential urinary retention. Prothiaden should not be used in patients with closed-angle glaucoma. Caution is advised when treating epileptic patients and those with cardiovascular disorders. Prothiaden should not be used with MAO inhibitors nor within 14 days of ceasing such treatment. It may modify the action of some CNS depressants, catecholamines and hypotensive agents. **Side Effects:** These are usually mild and normally controlled by reducing the dosage. The following have been reported: dryness of mouth, constipation, disturbed accommodation, orthostatic hypotension, palpitations, somnolence, tremor, headache. **Basic N.H.S. Price:** 28 × 75mg £4.00 as at 1st Oct. 1987 **Product Licence Numbers:** PL0014/5941. PL0014/0209. Boots Pharmaceuticals, Nottingham, England. Further information available on request. ETH 1324/2/90





ABRIDGED PRODUCT INFORMATION ▼ Indications: Symptomatic treatment of depressive illness. **Dosage: Adults:** initially 100-150mg daily. Increase if necessa
to 300mg daily in divided doses. Usual maintenance dose 150mg-250mg daily. **Elderly:** initially 25mg twice a day increasing under supervision after 5-7 days to 50mg three times dai
maximum. **Children:** not recommended. **Contra-indications:** Recent myocardial infarction; heart block; or other cardiac arrhythmias; mania; severe liver disease. **Precaution**
Narrow angle glaucoma; urinary retention; epilepsy; high suicidal risk patients (close supervision required). Use with caution in the elderly. Ability to drive a car and operate machine
may be affected. Use with caution in pregnancy and breast feeding. **Side effects:** Sedation, dry mouth, constipation, blurred vision, sweating, tremor, skin rash. Rarely, nausea, vomitir
diarrhoea, delayed micturition, impotence, breast enlargement and galactorrhoea (female) and tardive dyskinesia. Although not reported, other adverse effects associated with antidepressan
eg. blood dyscrasias, cholestatic jaundice, hypomania, cardiac arrythmias may occur. **Drug Interactions:** Do not give with or within 2 weeks of therapy with monoamine oxida
inhibitors. Interactions may occur with sympathomimetic agents, anti-hypertensives, barbiturates, alcohol, anaesthetics. **Overdosage:** Treatment is symptomatic and supportive. It shou
include gastric lavage and cardiac monitoring. **Legal Category:** POM. **Presentations and Basic NHS Prices:** Bottles of 100 heptagonal shaped tablets containi
Amoxapine: 25mg – white engraved "LL25" £10.89; 50mg – orange, scored, engraved "LL50" £18.16; 100mg – blue, scored, engraved "LL100" £30.27; 150mg – white, scored, engrave
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Lederle Laboratories, Cyanamid House, Fareham Road, Gosport, Hants PO13 0AS. *Asendis is a trademark. **REFERENCES: 1.** Bernstein JG. J Clin Psychiatry Monograph
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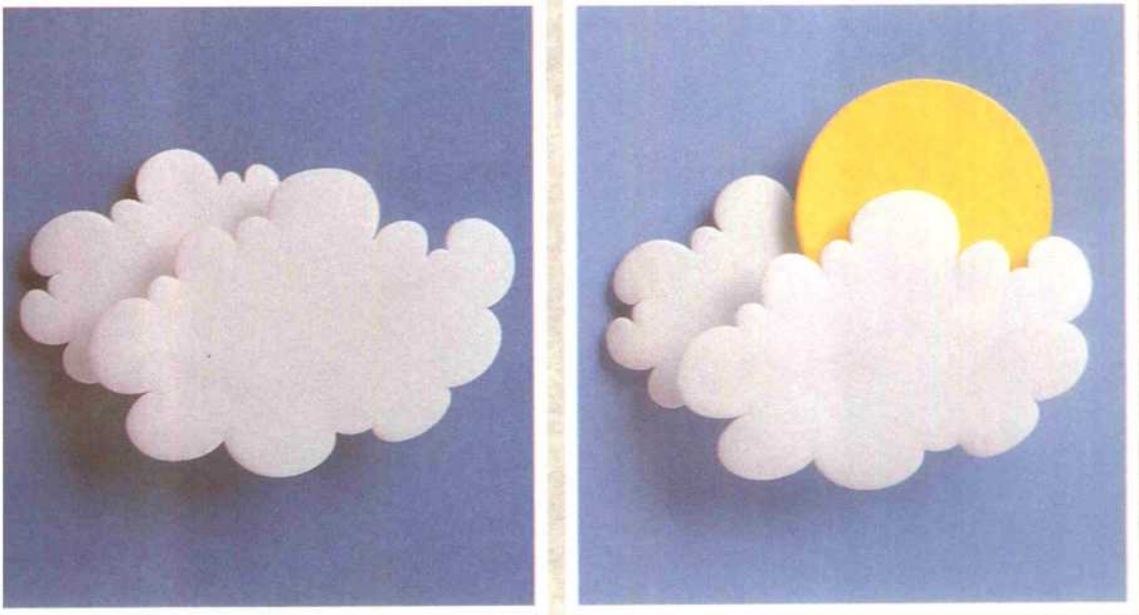

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An Analysis of Social Competence in Schizophrenia

ALAN S. BELLACK, RANDALL L. MORRISON, JOHN T. WIXTED and KIM T. MUESER

Twenty-one schizophrenics with prominent negative symptoms were compared with 37 schizophrenics without them, 33 patients with major affective disorder and 20 non-patient controls on a battery of measures including a role-play test of social skills, the Social Adjustment Scale, and the Quality of Life Scale. The negative schizophrenics were most impaired on every subscale of each measure, followed in order by the non-negative schizophrenics, affective disorder patients, and non-patient controls. The social skill measures were not correlated with positive symptom levels, but were highly correlated with measures of community functioning. The results are consistent with the hypothesis that social dysfunction results from focal deficits in social skills.

Severe impairment of social functioning is one of the hallmarks of schizophrenia. Deterioration of social relations is one of the defining diagnostic criteria specified in DSM–III–R (American Psychiatric Association, 1987), and social isolation or withdrawal and marked impairment in major life role functioning are listed as prominent prodromal and residual symptoms. While there has been widespread agreement about the existence of severe social disability for some time, there is surprisingly little data on the precise nature or the basis of the dysfunction (Wallace, 1984).

The most prominent hypothesis is that social impairments are epiphenomena which result from other more basic symptoms of the disorder, such as negative or deficit symptoms. There is considerable evidence to suggest that such symptoms as avolition, anhedonia and alogia demarcate a distinct subtype of schizophrenia (Andreasen, 1985; Carpenter *et al*, 1985; Crow, 1985). Patients whose illness is characterised by prominent negative symptoms have an increased frequency of structural brain impairment and decreased intellectual functioning, as well as a poorer prognosis (Johnstone *et al*, 1978). They also tend to have poor pre-morbid social competence and impaired social relationships (Liddle, 1987; Johnstone *et al*, 1979).

These findings suggest that negative symptoms play a central role in social disability. This possibility has high face validity in regard to such symptoms as blunted affect, avolition, anhedonia, and anergia. However, other negative symptoms, such as asociality and alogia, seem to be as much reflections of social impairment as causes of it. Indeed, Carpenter *et al* (1988) recently distinguished between primary and secondary negative symptoms, the former representing basic and enduring aspects of the illness while the latter are consequences of other factors. Thus, secondary negative symptoms could result from social disability as well as vice versa. This dichotomy has important implications for understanding the nature of the disorder and its treatment, but it has not yet been systematically examined.

A second hypothesis about the basis of social impairment in schizophrenia is provided by the behavioural model of social skills (Bellack & Morrison, 1982; Liberman, 1982; Trower *et al*, 1978). According to this model, effective social performance requires the skill to perform the appropriate response, as well as the cognitive/perceptual ability to determine what response is appropriate and the motivation to perform this (McFall, 1982). Thus, social skills are seen as necessary (although not sufficient) to produce effective social performance. The second hypothesis suggests therefore that schizophrenics have focal deficits in such social skills, and previously it has been presumed that they either fail to learn these initially or lose them after long periods of hospitalisation or social isolation. Unfortunately, the existing literature provides no sound validation for the skills model or for determining the precise role of social skills deficits in lowered social competence. The literature on pre-morbid social competence and childhood adjustment documents that many schizophrenics have long-standing impairments in role functioning. However, these studies are primarily retrospective and cannot elucidate the reasons for the faulty performance (Zigler & Levine, 1981). It has frequently been demonstrated that social skills training, which is based on the skills model, increases skill level and improves overall functioning (Morrison & Wixted, 1989). This provides convergent validational support for the skills model, but does not demonstrate that pre-treatment deficits were responsible for impaired functioning or that improved functioning resulted from increased skill.

Although the most frequently cited source of support for the skills model is behavioural observations of patients engaging in social interactions, few such studies have reported separate data on a carefully diagnosed cohort of schizophrenics. Longabaugh *et al* (1966) found notable deficits in a sample of schizophrenic in-patients. However, their subjects had all been hospitalised for at least six years, and could have been suffering from institutionalisation syndrome rather than skill deficiencies. Argyle (1981) reported that schizophrenics have a variety of specific skills deficits, including inappropriate facial expression, gestures and posture, low rewardingness, and poor synchronising. Lindsay (1982) also found that schizophrenics have specific performance deficits, although his sample consisted of only three patients. However, Rutter (1977*a*,*b*; 1978), in a study of paralinguistic behaviour, speech patterning, and visual interaction patterns, found few differences between schizophrenics and matched groups of non-patients and patients with other diagnoses.

Despite its widespread acceptance, the evidence in support of the skills hypothesis is quite tenuous. Firstly, no studies have examined patients diagnosed according to current (DSM-III (American Psychiatric Association, 1980) or DSM-III-R) criteria. Secondly, it is not clear that schizophrenics have specific skill deficits, as opposed to a general impairment in social functioning which results from other aspects of the disorder, such as negative symptoms. Thirdly, it is also uncertain if the social impairments characteristic of schizophrenia are specific to the disorder, or are associated with other chronic disorders as well. The purpose of the current investigation was threefold: (1) to determine if schizophrenics are more socially impaired than other chronic patients or non-patients; (2) to compare the social competence of patients with and without negative syndrome; and (3) to examine the relationship of social skills to positive and negative symptoms. A secondary goal of the study was to examine the validity of role-play tests of social skills.

Method

Patients and controls

The subjects, who included 58 schizophrenic patients (21 with negative syndrome and 37 with non-negative syndrome), 33 patients with major affective disorder (29 bipolar, 4 unipolar), and 20 non-patient controls, were selected from in-patient admissions to the psychiatry service of the Medical College of Pennsylvania (MCP) at the Eastern Pennsylvania Psychiatric Institute (EPPI). Patients were considered for the study if they were 18–50 years-of-age, with no obvious evidence of organic brain syndrome, mental retardation, or alcohol or drug abuse. Affective disorder patients were required to have at least a six-month history of illness, so as to be comparable to the schizophrenics on chronicity. Patients were interviewed within several weeks of their index hospitalisation with the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1978) or the Structured Clinical Interview for DSM-III (SCID) (Spitzer & Williams, 1985) by a trained psychologist. psychiatrist or psychiatric nurse. Based on these interviews and hospital records, a consensus diagnosis was reached by the interviewer and one of the first two authors (AB or RM) in accordance with DSM-III-R criteria. Approximately 20% of the structured interviews were reviewed by a third clinician in order to provide an independent check on the reliability of diagnosis. There was a 100 per cent agreement on primary DSM-III-R diagnosis for this sample.

Non-patient subjects were recruited from the non-professional staff and surrounding community of the hospital. Non-patient volunteers were excluded from participation if they had a history of treatment for a psychiatric disorder. Groups were matched as carefully as possible on age, socioeconomic status (SES) (Hollingshead & Redlich, 1958), race, and sex. ANOVAs (on age, education) and χ^2 (on sex, race) were non-significant (NS), indicating that the groups were carefully matched. However, as most non-patient controls were employed, there was a

TABLE I

Demographic variables and information about course of disorder for patients and non-patients

	Schizophrenics		*Those with affective disorder*	*Non-patient controls*
	negative (n=21)	*non-negative (n=37)*	*(n=33)*	*(n=20)*
Age[1] (mean): years	30.3	32.8	34.8	32.9
Sex: male	12	22	18	7
female	9	15	15	13
Education (mean): number of years	11.8	12.0	13.1	12.8
SES[2]	4.7	4.7	4.1	3.0
Race: black	10	13	6	8
white	11	24	27	12
Age of onset of disorder (mean): years	21.3	21.8	24.3	–
Duration of disorder (mean): years	9.1	10.2	10.7	–
Current hospitalisation (mean): days	29.4	31.9	28.6	–

1. Patients included between 18 and 50 years-of-age.
2. Hollingshead & Redlich, 1958.

significant difference between them and the patient groups on SES. All subjects were paid for participation in the study.

Table I provides a summary of age, educational level, SES, race, and sex, as well as age at onset of disorder (i.e. first in-patient hospitalisation), duration of disorder, and duration of present hospitalisation for the groups. All patients were on medication at the time of testing. Overall, the patient samples are young, acute groups, with few hospitalisations before the index assessment.

Structured interviews

The diagnostic interviewer completed the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). All subjects then participated in a second structured interview with an interviewer who was blind to diagnosis. That interviewer rated the subject on the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982; Andreasen & Olsen, 1982), and on two measures of social role functioning in the community: the Social Adjustment Scale II (SAS) (Weissman & Bothwell, 1976; Weissman & Paykel, 1974), and the Quality of Life Scale (QLS) (Heinrichs *et al*, 1984). The SAS is a self-report and interviewer rating scale which yields scores on five dimensions: 'work adjustment', which includes adjustment as a student or homemaker; 'household adjustment', which deals with relationships with household members; 'external family adjustment', or relationships with relatives outside of the household; 'social and leisure adjustment'; and 'general adjustment', which is an overall measure. The QLS is a 21-item interviewer rating scale which provides ratings on four dimensions: 'interpersonal relations', which judges capacity to form relationships as well as the extent of social interactions; 'instrumental role functioning', which focuses primarily on occupational, student, or homemaker roles; 'intrapsychic foundations', which relates to cognitive, affective, and motivational functioning; and 'common objects and activities', which assesses participation with the objects and activities of every day life (e.g. reading newspapers, shopping, possession of a wallet, keys, watch, etc.).

Interviewers were trained and supervised by the first two authors. Approximately 25% of all interviews were rated by a second, independent rater. Reliability was satisfactory for each subscale of each measure (reliability coefficients range $r=0.77$–0.91) with the exception of 'household adjustment' on the SAS ($r=0.64$).

Behavioural observations

Social skill is a construct which has defied easy measurement. Characteristically, it is defined operationally by performance on an analogue test of social interaction (e.g. a role play or structured conversation). Adequate performance on the test implies that the individual has the requisite skills in his/her repertoire, although other factors may interfere with performance in real life interactions. An individual who does not perform adequately may not possess the requisite skills, or may fail to manifest them due to confounding factors (e.g. anxiety about being videotaped). Given these limitations, behaviour on these tasks must be interpreted cautiously. However, they have been shown to be quite useful in evaluating the effects of social skills training and in discriminating high- and low-skill groups from diverse diagnostic populations (Bellack, 1979; 1983).

All subjects participated in a role-play test of social skills which was videotaped and retrospectively rated on a number of specific behavioural components. Subjects were seated in a videotape studio with a research assistant who portrayed an interpersonal partner. They enacted 12 social encounters in which the subject was required to either initiate a conversation, resist unfair treatment, or express appreciation for something the confederate did or said. Each interaction continued through three verbal interchanges (i.e. the subject was required to make at least three responses to confederate prompts).

Role-play enactments were subsequently rated on appropriateness of: gaze, speech duration, meshing (smoothness of turn taking and conversational pauses), affect, and two verbal content measures (request/compliance and praise/appreciation). Independent ratings were made of overall social skill. All ratings were made by research assistants who were blind to subjects' group status. Raters were trained on a library of videotapes from our previous research. They first learned to match criterion ratings, and then practised rating independently until each behavioural category was rated with a reliability of at least $r=0.80$. Initial data tapes from this protocol were rated independently by the primary raters, and then reviewed jointly by the raters and one of the authors to further ensure the accuracy and consistency of the ratings. One third of the videotapes (drawn proportionately from each subject group and different time points) were scored by an independent rater to provide a reliability check. Reliability was high for all categories (Pearson correlation coefficients range, 0.74–0.89).

Procedure

Clinical records of all new admissions to the MCP/EPPI in-patient units were reviewed by a research staff member, and appropriate patients were then screened using a SADS or the SCID to determine the diagnosis. Patients accepted into the study participated in the interview measures and role-play test on two separate days within one week of the diagnostic interview. Testing was initiated after the research team and the attending physician concurred that acute symptoms had remitted sufficiently for the patient to leave the ward and complete the research tasks. Non-patient subjects were similarly scheduled to complete the interview and role-play test measures within a one-week period.

Data analysis plan

The data analysis consisted of a series of steps designed to first categorise and describe our sample, and then test the following hypotheses: (1) negative schizophrenics will be more socially impaired than non-negative patients, who will not differ from bipolars, but all three groups will be impaired in relation to non-patient controls; (2) social competence measures will have only a moderate correlation with symptom measures (suggesting that social dysfunction is not solely a by-product of either positive or negative symptoms); (3) role-play measures of social skills will be related to role functioning in the community.

Results

Subclassification of schizophrenics

Schizophrenic subjects were retrospectively categorised as negative or non-negative according to the criteria of Andreasen (1982). Negative subjects were characterised by scores of four (marked) or five (severe) on two or more categories on the SANS. As all subjects were receiving neuroleptics and acute positive symptoms were at least partially remitted, we did not separately classify subjects as having positive schizophrenia. Hence, the non-negative group includes patients who might fit Andreasen's positive or mixed categories. Twenty-one patients met the criteria for negative schizophrenia and 37 were classified as non-negative. The negative group had a mean score of 3.27 (range = 9–24) on the five SANS scales, compared to a mean of 1.67 (range = 1–15) for non-negatives. Analyses of variance indicated that the negative group exhibited significantly more symptoms on each of the five SANS categories: 'affective flattening', $F(1,51\ \text{d.f.})=26.50$, $P<0.001$; 'alogia', $F(1,51\ \text{d.f.})=13.94$, $P<0.001$; 'avolition-apathy', $F(1,51\ \text{d.f.})=60.59$, $P<0.001$; 'anhedonia-asociality', $F(1,51\ \text{d.f.})=34.27$, $P<0.001$; and 'inattention', $F(1,51\ \text{d.f.})=8.1$, $P<0.005$.

Medication and symptoms

All schizophrenics were receiving neuroleptics at the time they were assessed. Some of the common side effects of neuroleptics, including akinesia and pseudoparkinsonism, can result in impairments which are similar to negative symptoms. As a partial check on the extent to which the negative symptoms of our subjects may have been drug-induced, we compared the dosage levels of patients in the two schizophrenic groups. Dosages were first converted to chlorpromazine equivalents (Davis & Glerl, 1984). Negative symptom patients were receiving a mean of 891.67 mg per day compared with 883.80 mg per day for non-negative ones. This difference was not significant ($t(49\ \text{d.f.})=0.05$). Furthermore, correlations between SANS scores and dosage level were uniformly low and non-significant (range −0.10–0.03).

Descriptive statistics and results of analyses of variance for BPRS summary scores are presented in Table II. As expected, the negative schizophrenic group scored significantly higher than the other three groups on the 'anergia' factor, which substantially reflects negative symptoms. The two schizophrenic groups did not differ on any other scale, indicating that the negative group did not exhibit more symptoms uniformly. The non-negative and negative schizophrenics had mean scores of 12.41 and 14.14 respectively on the BPRS 'thought disorder' scale, indicating that most of these subjects were still actively psychotic at the time they were assessed. The affective disorder patients were less thought disordered than either of the schizophrenic groups at the time of assessment ($x=9.15$, $P<0.05$), but 88% of them were psychotic at the time of admission, and 67% continued to exhibit psychotic symptoms at the time of testing (based on BPRS scores of four or more on any of the individual 'thought disorder' items).

Group differences in social competence

The basic strategy for comparing social functioning of the four groups was to conduct separate two-way, repeated

TABLE II
Descriptive statistics, F ratios, and Tukey comparisons for the Brief Psychiatric Rating Scale (BPRS)

	Schizophrenics				*Those with affective disorder (A) (n=33)*		*Non-patient controls (C) (n=20)*			
	negative (NS) (n=21)		*non-negative (S) (n=37)*							
Subscale of BPRS	*Mean (s.d.)*	*Range*	*Mean (s.d.)*	*Range*	*Mean (s.d.)*	*Range*	*Mean (s.d.)*	*Range*	F^1	*Tukey*
Anxiety/ depression	8.47 (4.11)	4–18	10.08 (3.68)	4–17	8.47 (3.48)	4–20	7.40 (3.14)	4–14	2.69*	S>C
Anergia	10.34 (4.45)	4–19	7.95 (3.60)	4–18	5.18 (2.04)	4–12	4.43 (0.84)	4–7	18.02**	NS S>A,C NS>S
Thought disorder	14.14 (5.62)	4–25	12.41 (4.36)	4–23	9.15 (4.29)	4–19	4.60 (1.19)	4–8	21.56**	NS S,A>C NS S>A
Activation	6.79 (3.08)	3–13	6.30 (2.26)	3–12	6.73 (3.00)	3–13	3.60 (0.88)	3–6	7.85**	NS S,A>C
Hostility	7.86 (4.09)	3–19	7.68 (3.63)	3–14	6.21 (2.86)	3–12	4.05 (1.47)	3–7	6.77**	NS S>C
Total	44.5 (11.1)	23–64	42.1 (9.6)	24–57	34.5 (8.0)	17–51	23.0 (4.9)	17–36	27.05**	NS S,A>C NS S>A

*$P<0.05$, **$P<0.0001$.

1. 3, 107 d.f.

measures analyses on the role-play data, the SAS, and the QLS, in which group served as a between-subjects variable, and the subscales of the three measures of social functioning served as within-subjects variables. The statistic used was a MANOVA approach to repeated measures analysis of variance (Bray & Maxwell, 1985), which was calculated by SPSS Advanced version V2.0 (Norusis, 1988). These analyses allowed us to simultaneously examine both overall group differences within each domain and possible interaction effects, while controlling the number of independent tests conducted. As the subscales on the various instruments varied somewhat in scoring range and format, raw scores were normalised and converted to z scores for entry into the MANOVA. Multivariate effects on each analysis were tested with Pillai's trace statistic. Because of the z transformation, each social competence subscale had the same mean and standard deviation when collapsed across subject groups. Therefore, the resultant F ratios were meaningless and are not discussed below.

Role-play test data

Previous research on social skill suggests that the components of role-play behaviour are substantially related to overall social competence, but that they do not individually account for a significant proportion of variance (Conger & Farrell, 1981; Romano & Bellack, 1980). Consequently, the component scores were summed for each subject across non-verbal (gaze, length, meshing, and affect) and verbal (praise/appreciation and request/compliance) behaviour categories. This meant that the within-subjects variables on the role-play MANOVA consisted of overall social skill as well as non-verbal and verbal skill. The group effect was highly significant (F [3, 102 d.f.] $=23.83$, $P<0.001$), and there was a significant group by subscale interaction (F [6, 204 d.f.] $=2.85$, $P<0.05$). As indicated in Table III, the order of means was the same for each of the variables: negative schizophrenics exhibited the least skill, followed by non-negative schizophrenics, affective disorder patients, and non-patient controls respectively. Tukey *post hoc* tests (across the three skill variables) indicated that the patient groups each exhibited significantly less skill than the non-patient controls ($P<0.05$), and the negative schizophrenics performed significantly worse than both the non-negatives and the affective disorder patients ($P<0.05$). The latter two groups were not significantly different.

The significant interaction was examined by conducting one-way, repeated measures ANOVAs on each group. As these analyses were conducted on z scores generated separately for each skill category, they reflect comparative standing of the groups on each measure rather than absolute comparisons between skill levels in each domain. The only one of the four analyses to reach significance was that for non-patient controls (F [2, 17 d.f.] $=6.07$, $P<0.001$). They were rated as proportionately more skilful than the patient groups on the overall measure than on either of the two component categories.

SAS and QLS data

Results for the QLS and SAS (Table III) were similar to the results for the role-play test. On each subscale in each of these instruments, negative schizophrenics were the most impaired, followed in order by non-negative schizophrenics, affective disorder patients and non-patient controls. The MANOVA on the QLS yielded a highly significant group effect (F [3, 102 d.f.] $=68.72$, $P<0.001$) and a significant group by subscale interaction (F [9, 306 d.f.) $=2.99$, $P<0.05$). Tukey *post hoc* tests on group means indicated that all three patient groups scored significantly worse than the non-patient controls. The negative schizophrenics were rated significantly worse than the other two patient groups,

TABLE III

Descriptive statistics for social functioning measures (role-play, SAS and QLS)

	Schizophrenics		*Those with*	*Non-patient*
	negative	*non-negative*	*affective disorder*	*controls*
	Mean[1] *(s.d.)*	*Mean*[1] *(s.d.)*	*Mean*[1] (s.d.)	Mean[1] *(s.d.)*
Role-play test of social skills				
Non-verbal component	0.64 (1.00)	0.10 (0.60)	−0.17 (0.40)	−0.56 (0.31)
Verbal component	0.46 (0.75)	0.23 (0.86)	−0.07 (0.69)	−0.69 (0.41)
Overall ratings	0.76 (0.86)	0.29 (0.80)	−0.17 (0.71)	−1.14 (0.67)
Quality of Life Scale				
Interpersonal relations	−1.00 (0.47)	−0.23 (0.70)	−0.06 (0.76)	1.53 (0.60)
Role functioning	−0.71 (0.39)	−0.22 (0.74)	−0.06 (1.00)	1.54 (0.37)
Intrapsychic foundations	−1.26 (0.53)	−1.19 (0.63)	0.15 (0.75)	1.45 (0.40)
Common objects & activities	−0.61 (0.95)	−0.07 (0.75)	−0.04 (0.97)	1.23 (0.75)
Social Adjustment Scale				
Work adjustment	0.98 (0.21)	0.29 (0.55)	0.10 (0.87)	−1.39 (0.57)
Household adjustment	0.85 (0.57)	0.27 (0.57)	0.14 (0.92)	−1.35 (0.83)
External Family adjustment	0.83 (0.60)	0.28 (0.88)	0.23 (0.74)	−1.37 (0.52)
Social/Leisure adjustment	0.90 (0.32)	0.29 (0.56)	0.20 (0.77)	−1.65 (0.63)
General adjustment	0.92 (0.42)	0.24 (0.70)	0.11 (0.69)	−1.64 (0.57)

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1. The means were calculated using z score transformations.

which did not differ from one another. As with the role-play data, the significant interaction was examined with a series of one-way, repeated measures ANOVAs. The results indicated that the interaction was accounted for by the low scores for negative schizophrenics on the intrapsychic foundations subscale (F [3, 17 d.f.] $=5.94$, $P<0.001$). This scale, which consists of items such as motivation, curiosity, and anhedonia, is more a measure of negative symptoms *per se* than of 'quality of life'. Consequently, it is not surprising that negative schizophrenics would be rated differentially lower on this scale than on the other subscales.

Each of the scales on the SAS can be coded 'not applicable' if it is not relevant to the subject's current life situation. A majority of subjects in each of the three patient groups received such scores for either the 'work adjustment' or 'external family adjustment' scales (e.g. they were not working, did not have any contact with relatives, etc.). Consequently, the MANOVA was conducted on the remaining three scales. There was a highly significant group effect (F [3, 89 d.f.] $=62.27$, $P<0.001$), but the interaction was not significant. As with the role play and QLS, Tukey tests indicated that the three patient groups were functioning significantly more poorly than the non-patient controls, and the negative schizophrenics were significantly more impaired than either of the other two patient groups. Univariate ANOVAs were conducted on those patients who did receive scores on the 'work' and 'external family' scales, and the three patient groups were rated significantly lower on both: external family, $F(3, 91 \text{ d.f.})=30.23$, $P<0.001$; work $F(3, 75 \text{ d.f.})=45.37$, $P<0.001$. The negative schizophrenics were significantly worse than the other two patient groups on 'work adjustment', but did not differ on 'external family'.

Social functioning and symptoms

Hypothesis two proposed that social dysfunction was not solely a by-product of either positive or negative symptoms. In order to examine this, Pearson correlation coefficients were calculated between the social functioning measures (role play, SAS, and QLS) and the symptom measures (BPRS and SANS) for all schizophrenics combined. The results for positive symptoms, as reflected by the BPRS, appear in Table IV. The correlations between BPRS factor scores and role-play measures were uniformly low and non-significant (range −0.18–0.25), indicating that there was little relationship between positive symptoms and social skills. The correlations with the SAS and QLS were more variable. While most of the correlations were non-significant, there did appear to be a consistent relationship between several BPRS subscales and adequacy of interpersonal relationships, as reflected on both the SAS and QLS.

A similar pattern was reflected on the SANS, although the correlations were consistently higher (see Table V). The correlations between SANS and role-play measures ranged from 0.08 to 0.55. Not surprisingly, affective flattening had a notable impact on non-verbal skills as did anergia in the BPRS. For the most part, SANS ratings accounted for less than 10–15% of the variance in role-play behaviour which is consistent with the BPRS anergia ratings. In contrast, SANS scales were highly correlated with role functioning (i.e. SAS and QLS), in some cases accounting for more than 50% of the variance.

Validity of role-play measures

In order to examine hypothesis three (the validity of the role-play test), a series of Pearson correlations was

TABLE IV

Pearson correlation coefficients between social functioning measures (role-play, SAS and QLS) and a symptom measures (BPRS)

	Brief Psychiatric Rating Scale					
	Anxiety/ depression	*Anergia*	*Thought disorder*	*Activation*	*Hostility*	*Total*
Role-play test of social skills						
Verbal components	−0.17	−0.02	0.00	−0.02	0.07	−0.04
Non-verbal components	−0.03	0.24	0.08	0.16	−0.03	0.11
Overall ratings	−0.16	0.18	0.17	0.17	0.07	0.16
Quality of Life Scale						
Interpersonal relations	−0.03	−0.05	−0.44**	−0.40*	−0.38*	−0.49**
Role functioning	0.10	−0.19	−0.17	−0.30	−0.22	−0.29
Intrapsychic foundations	0.09	−0.27	−0.43**	−0.30	−0.35*	−0.48**
Common objects & activities	−0.07	−0.08	−0.12	−0.05	−0.20	−0.20
Social Adjustment Scale						
Work adjustment	−0.41*	0.37*	0.09	0.28	0.07	0.11
Household adjustment	−0.26	0.17	0.32	0.37*	0.13	0.27
External family adjustment	−0.07	0.20	0.29	0.22	0.42	0.40*
Social/leisure adjustment	−0.18	0.17	0.26	0.39*	0.35*	0.35*
General adjustment	−0.25	0.17	0.23	0.30	0.34*	0.28

*$P<0.01$, **$P<0.001$.

TABLE V
Pearson correlation coefficients between social functioning measures (role-play, QLS AND SAS) and a symptom measure (SANS)

	Scale for the Assessment of Negative Symptoms				
	Affective flattening	*Alogia*	*Avolition-apathy*	*Anhedonia-asociality*	*Inattention*
Role-play test of social skills					
Verbal components	0.19	0.08	0.18	0.09	0.12
Non-verbal components	0.55**	0.38*	0.29	0.36*	0.29
Overall ratings	0.36*	0.34*	0.46**	0.32*	0.32*
Quality of Life Scale					
Interpersonal relations	−0.54**	−0.22	−0.53**	−0.83**	−0.36*
Role functioning	−0.28	−0.24	−0.53**	−0.43**	−0.33*
Intrapsychic foundations	−0.58**	−0.48**	−0.75**	−0.74**	−0.52**
Common objects & activities	−0.08	−0.28	−0.40**	−0.16	−0.18
Social Adjustment Scale					
Work adjustment	0.33	0.36*	0.72**	0.58**	0.44*
Household adjustment	0.37*	0.19	0.59**	0.64**	0.16
External family adjustment	0.39*	0.02	0.21	0.48**	0.51**
Social/leisure adjustment	0.52**	0.36*	0.58**	0.79**	0.46**
General adjustment	0.47**	0.34*	0.54**	0.66**	0.50**

*$P<0.01$, **$P<0.001$.

TABLE VI
*Pearson correlations between role-play test and QLS and SAS for all subjects**

	Role play test of social skills		
	Verbal components	*Non-verbal components*	*Overall ratings*
Quality of Life Scale			
Interpersonal relations	−0.42	−0.47	−0.58
Role functioning	−0.42	−0.38	−0.53
Intrapsychic foundations	−0.50	−0.57	−0.70
Common objects & activities	−0.36	−0.35	−0.40
Social Adjustment Scale			
Work adjustment	0.43	0.54	0.62
Household adjustment	0.36	0.47	0.60
External family adjustment	0.37	0.46	0.43
Social/leisure adjustment	0.41	0.46	0.59
General adjustment	0.43	0.47	0.59

*All correlations significant at $P<0.001$.

calculated between role-play measures and scores on the SAS and QLS for all subjects combined. The resulting correlation matrix is presented in Table VI. The correlations were uniformly high and significant (range 0.35–0.69; the negative sign reflects the inverse scaling of the QLS).

Discussion

The results of this investigation provide strong support for the contention that schizophrenics have pronounced deficits in social competence. They were substantially impaired on verbal, non-verbal, and overall ratings of social skill, as well as on interview ratings of role functioning. They scored significantly worse than non-patient controls on each measure. They also were consistently rated as more impaired than the affective disorder patients, although the differences were not significant for the non-negative subsample. This is the first study in which a carefully diagnosed cohort of schizophrenics was clearly shown to have marked social disability in comparison with both non-patients *and* a matched group of patients with another chronic disorder.

The results also indicate that the impairments in social functioning are not simply secondary consequences of negative or positive symptoms. The correlations between the SANS and role functioning measures (SAS and QLS) were consistently high and significant, which is consistent with the hypothesis that negative symptoms can result in social impairment. However, the analyses of variance distinguished between patients with and without high levels of negative symptoms. Patients with prominent negative symptoms consistently showed the greatest impairments, but non-negative patients also exhibited substantial deficits on each measure. These data indicated that poor social functioning can occur in the absence of negative symptoms.

The SANS, SAS, and QLS were all rated by the same interviewer, in part to ensure that the SANS rater had adequate information to make accurate judgements. This raises the possibility that the correlations between the three may be somewhat inflated by halo effects. However, two factors vitiate this concern. The anergia subscale of the BPRS was highly correlated with the SANS total score ($r=0.46$, $P<0.001$). As the BPRS was rated by a different interviewer, this correlation provides an independent check on the validity of the SANS ratings. Similarly, independent ratings of the SANS, SAS, and QLS were conducted to verify inter-rater reliability. The magnitude of these reliability coefficients (range $r=0.77$–0.91) also suggests that ratings of the two domains were distinct and valid.

The role-play test provides data on social competence from a different domain: behavioural observation. Both the ANOVAs and the correlations suggest that negative symptoms could have a deleterious effect on social skill. However, once again, non-negative patients also exhibit marked skill deficits and the correlations between the SANS and the role-play measures were modest in comparison to those between the former and the SAS and QLS. Moreover, the primary effect of negative symptoms on social skill components seemed to be on non-verbal behaviour, possibly reflecting the concordance between such behaviour and ratings of anergia. These data suggest that negative symptoms have a more pronounced effect on performance of social roles than on the social skills required for effective functioning. Of course, these correlational data do not specify causality or the direction of effects. Negative symptoms could be a manifestation of social impairment, as well as vice versa. Moreover, both phenomena could be mediated by some third variable. However, the data do demonstrate that social skill is not simply a result of negative symptoms.

Pearson's correlations indicate that positive symptoms do not have a uniform effect on social behaviour. Some symptoms (e.g. hostility, suspiciousness and excitement) apparently have a highly deleterious effect on interpersonal relationships but core psychotic symptoms (e.g. hallucinations, delusions) do not have a marked effect. Similar findings have been reported by Johnstone *et al* (1979) and Liddle (1987). Previous research suggests that non-negative schizophrenia is often associated with good social adjustment between episodes (Andreasen, 1985). The validity of that conclusion apparently depends on which symptoms are examined. Schizophrenics may sometimes be able to control or compensate for delusions and hallucinations during social interactions, but cognitive and affective symptoms have a more deleterious effect.

While non-negative patients were more socially competent than negative patients, they were definitely *not* functioning adequately. They were significantly impaired in comparison to non-patient controls on almost every measure. It is possible that their functioning would improve as symptoms continued to remit. However, it seems unlikely that social dysfunction of the magnitude found would totally resolve. Moreover, the affective patients were also significantly impaired, despite having a different set of symptoms. These data further support the hypothesis that social dysfunction is not always secondary to a specific set of schizophrenic symptoms. It should also be pointed out that many of our subjects were suffering from some degree of positive *and* negative symptoms. This combination may be more pernicious than either alone, producing high levels of distress and robbing patients of the capacity to effectively cope with their discomfort.

Both positive and negative symptoms were highly correlated with role functioning, but had little relationship with social skill. Conversely, social skill was highly correlated with role functioning. Together, these findings provide considerable support for the social skills hypothesis. Social skill, as reflected by role-play behaviour, appears to have a significant effect on social functioning in the community, independent of other symptoms of the disorder. This conclusion is consistent with the hypothesis proposed by Strauss *et al* (1974) that social competence represents an independent component of schizophrenia, orthogonal to both positive and negative symptoms. By 'independent' we do not imply that that social functioning is unaffected by positive and negative symptoms: our data strongly argue to the contrary. However, social skill deficits can also result in social dysfunctions, including phenomena such as alogia and asociality which present as negative symptoms. Carpenter *et al* (1988) refer to such effects as 'secondary' negative symptoms. Similarly, in some cases 'thought disorder' might better be conceptualised as a deficit in social cognition or a communication problem (Thomas *et al*, 1987; Cutting & Murphy, 1988). Thus, the poorer role functioning of some of the negative schizophrenics in this study might have resulted from more extensive skill deficits rather than from negative symptoms *per se* (i.e. 'primary' negative symptoms).

The data provide strong support for the validity of the role-play test. Role play performance was, to a considerable extent, independent of core psychotic symptoms and was highly related to independent measures of social functioning and interpersonal relationships in the community. Previous research has suggested that role-play behaviour is not a direct parallel of behaviour in the natural environment (Bellack, 1979, 1983). However, the current study documents that role-play behaviour provides an excellent reflection of overall social functioning in the community. The ratings of 'overall social skill' in particular provide a cost-efficient way of assessing a critical aspect of functioning which is not well tapped by more traditional assessment procedures.

Current data are not adequate to determine the aetiological factor underlying schizophrenics' social impairment. Problems of social learning, as proposed by the social skills model, is but one possibility: schizophrenia characteristically strikes during young adulthood, preventing the patient from mastering critical social/developmental tasks associated with heterosexual and job skills, separation from family, etc. Conversely, there is evidence that some interpersonal deficits may result from a structural or functional brain impairment. For example, schizophrenics have been reported to have marked deficits in facial affect recognition, which might result from a right-hemispheric lesion or imbalance in hemispheric dominance (Morrison *et al*, 1988). Data on early childhood disturbances and poor pre-morbid social functioning suggests the possibility of an insidious pathological process, rather than a problem in learning (Lewine *et al*, 1978; Strauss *et al*, 1974). In keeping with recent thinking on the heterogeneity of the disorder, it may well be that there are multiple possible pathways to social dysfunction. While data from the current investigation cannot resolve this issue, by documenting the relative independence of social skills deficits they provide substantial justification for further research on both the nature and aetiology of such deficits.

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Sex Differences in the Familial Transmission of Schizophrenia

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The hypothesis that schizophrenic men have a lower familial risk for schizophrenia than schizophrenic women was tested using the DSM–III-diagnosed samples of the Iowa 500 and non-500 family studies. Survival analyses were used to test for differences in the risk for schizophrenia and spectrum disorders, for sex of proband and sex of relative, controlled for fertility effects and ascertainment bias. Male and female relatives of schizophrenic men had a significantly lower risk for schizophrenia, schizophreniform, and schizoaffective disorders than relatives of schizophrenic women. However, the effect was not significant for the full spectrum nor when analysed by sex of relative. Sex differences in the risk for other psychiatric disorders among relatives of schizophrenic probands were not significant.

The familial nature of at least some forms of schizophrenia is well established in the literature. The morbidity risk for schizophrenia among first-degree relatives has been found to range from 3% to 15% (Gottesman & Shields, 1982; Guze *et al*, 1983; Kendler *et al*, 1985). It is generally accepted that this risk does not vary by sociodemographic characteristics of the probands, in particular by sex (Gottesman & Shields, 1982; Wyatt *et al*, 1988). However, recent literature (Bellodi *et al*, 1986; Shimizu *et al*, 1987) has suggested that the risk may differ by sex of proband and/or sex of relative. This is consistent with a wealth of information demonstrating significant differences between schizophrenic men and women: schizophrenic men have been found to have an earlier age at onset, poorer pre-morbid history, more perinatal complications, more deficit symptoms, poorer course, and poorer response to neuroleptics (Mednick *et al*, 1978; Seeman, 1985; Pearlson *et al*, 1985; Turner *et al*, 1986; Goldstein & Link, 1988; Lewine, 1988; Lewis, 1989). Furthermore, a few studies have shown that schizophrenic men and women have different patterns of structural and functional brain abnormalities and neurological deficits, some of which suggest dysfunction in the left hemisphere or more diffuse dysfunction among the men (Flor-Henry, 1978; Gur *et al*, 1985; Geschwind & Galaburda, 1985; Nasrallah *et al*, 1986).

Taken together, findings on sex and schizophrenia suggest that schizophrenic men and women may be at different risks for expressing particular forms of the illness. Thus, it may also follow that there are sex differences in the familial risk for schizophrenia. Given past literature (cited above) suggesting that schizophrenic men experience more perinatal complications and a different pattern of structural and functional brain abnormalities, we hypothesised that there may be a subgroup of schizophrenic men who have a lower family morbidity risk, given that their clinical picture may *in part* be due to environmental insults. This is a plausible hypothesis given earlier work demonstrating significant inter-relationships between sex, perinatal complications or other early physical trauma, deficit symptoms, and lack of family history of schizophrenia (Pearlson *et al*, 1985; Turner *et al*, 1986).

Early studies found that concordance rates among female monozygotic (MZ) and dizygotic (DZ) twins were higher than among male MZ or DZ twins (Rosanoff *et al*, 1934; Slater, 1953; review by Rosenthal, 1962). However, twin studies in the 1960s and '70s found no significant differences (Kringlen, 1968; Gottesman & Shields, 1972; Fischer, 1973). It was suggested that this discrepancy may have been due to sampling bias; for example earlier samples contained too many females (Gottesman & Shields, 1972). Thus, when consecutive admissions were used, no differential sex-specific concordance occurred. However, it is unclear what the status of sex-specific concordance among twins would be if current diagnostic criteria for schizophrenia were used. Earlier criteria were broad enough to include a substantial proportion of affective disorders, which are more frequently diagnosed in women (Lewine *et al*, 1984; Goldstein & Link, 1988). If current diagnostic criteria are used, schizophrenic men are more frequently admitted to hospital than schizophrenic women (Goldstein, 1988; Lewine, 1988; Angermeyer *et al*, 1989). Thus use of consecutive admissions may oversample men, whereas in earlier studies women were oversampled.

Only a few recent studies (Loyd *et al*, 1985; Bellodi *et al*, 1986; Shimizu *et al*, 1987) have tested for the effect of sex on the family morbidity risk for DSM-III-diagnosed schizophrenia-related disorders (American Psychiatric Association, 1980). Shimizu *et al* (1987) were the only researchers to focus on DSM-III schizophrenia alone. They found a significantly higher rate of schizophrenia among mothers and fathers of female probands than among those of male probands, but not among the siblings. However, no age correction was used, and thus siblings may not have passed through the period of risk. Loyd *et al* (1985) found no significant sex differences in the risk for 'atypical schizophrenia' among first-degree relatives, defined as schizophreniform, schizoaffective and paranoid disorders, atypical psychosis, and schizotypal personality disorder. In contrast, Bellodi *et al* (1986) demonstrated that the risk for schizophrenia spectrum disorders in first-degree relatives of schizophrenics was significantly higher in female probands than male probands. In addition, they found that female relatives of probands of paranoid subtype who were HLA A1 and CRAG A1 positive were at higher risk than any other group. However, in the Bellodi study, relatives were not personally interviewed. As the authors noted, the family history method tends to underestimate morbidity risk. This method is particularly problematic for identifying spectrum disorders, such as schizotypal personality disorder. Further, it is unclear what differential effects the sex of the relative may have on the identifier's memory or perception of illness in their relatives.

In the study reported here, relatives were personally interviewed, and tests of hypotheses were adjusted for confounding factors, such as variable ages of onset and fertility effects. The study tests the hypothesis that first-degree relatives of schizophrenic men are at lower risk for schizophrenia and spectrum disorders than relatives of schizophrenic women.

Specificity of the findings was tested by examining sex differences in the family morbidity risk for other axis I and II disorders.

Method

Procedure

Data for this study consist of the double-blind, retrospective cohort studies conducted in Iowa in the 1970s, the Iowa 500 and non-500 family studies. Details of the sample selection and follow-up procedures are described elsewhere (Morrison *et al*, 1972; Tsuang & Winokur, 1975). Briefly, probands for this study were selected from a blind review of index admission and follow-up records and interviews of 510 consecutive admissions with a clinical diagnosis of schizophrenia to the Iowa Psychopathic Hospital from 1934 to 1944. Probands were rediagnosed using DSM-III criteria by two expert psychiatrist diagnosticians (Kendler *et al*, 1985). The criterion limiting age of onset to 45 years was eliminated, as in DSM-III-R (American Psychiatric Association, 1987).

First-degree relatives of schizophrenic probands were also blindly diagnosed using DSM-III criteria based on a blind, personal structured psychiatric interview developed by Tsuang *et al* (1980) ($n = 642$), hospital records obtained from a systematic search of the five Iowa public psychiatric hospitals ($n = 55$), or both hospital records and personal interviews ($n = 28$). Axis I and II disorders were assessed in relatives. Sex differences in the risk for schizophrenia as well as the 'full spectrum' (schizophrenia, schizophreniform, schizoaffective, paranoid, atypical psychosis, and schizotypal personality disorder) in relatives of probands were also assessed. Reliability of diagnoses was very good as indicated by an overall kappa of 0.88 (Kendler *et al*, 1985). Relatives with only hospital records were included in order to maximise the available information even though risk estimates for relatives may consequently be high, but comparisons of patterns of illness including and excluding these cases showed similar results (Kendler *et al*, 1985). There were 253 out of the 332 schizophrenic probands for whom we had clinical information on relatives.

Normal controls ($n = 318$) were sampled from patients undergoing appendectomies and herniorrhaphies from the Iowa general hospital from 1938 to 1948, and matched by age, sex, and status in terms of health insurance. All controls were screened for psychiatric symptoms. Control subjects had 1359 siblings and 988 children. Information on the controls' family size was used to test for fertility effects.

Although several hypotheses have been previously examined with these data, no one has investigated the effect of sex on the familial tranmission of schizophrenia. Survival analysis (Lee, 1980; Thompson & Weissman, 1981) was used to estimate differences in morbidity risk for relatives of male versus female probands. Survival analysis, using the product limit or Kaplan–Meier method, estimates the probability that an individual will develop an illness at a particular age. This method is advantageous because it controls for variable ages of onset and confounding due to mortality in estimating morbidity risks, and makes full use of longitudinal data if observation periods vary. A Wilcoxon χ^2 was used to test for differences between survival curves. Tests were conducted to examine the effect of sex of the proband and sex of the relative on morbidity risk estimates. Finally, sex differences in morbidity risks for other disorders among relatives of schizophrenic probands were tested using survival analysis.

We compared other methods to estimate morbidity risks, for example Strömgren's abridged method (Goldstein *et al*, 1990) and Weinberg's (Slater & Cowie, 1971), and results were similar, probably because almost all relatives in this sample were past the period of risk. Thus, under these conditions, cruder methods of age adjustment yield similar results to survival analysis that controls for variable ages of onset and mortality.

Probands and relatives

There were 332 DSM-III schizophrenics (171 men, 161 women), 99% non-Hispanic white. On admission, they had a mean age of 27 years, 48% had completed secondary education, and 32% had had some tertiary education; 70% had never married, and 27% were currently married. Patients had a wide range of occupational statuses on admission: 25% were in unskilled, semiskilled, or skilled labour, 21% were in clerical, management, or professional jobs, 20% were homemakers, 11% were students, and 16% were unemployed.

Eighty-two per cent of the probands had had no previous admissions. Forty-two per cent had been ill for less than six months, 8% had been ill for between six months and one year, and 51% had been ill for over one year before first admission. Fifty-seven per cent of all probands had had a poor pre-morbid history. Age of onset was reliably available for 319 (mean 26.1 ± 7.5 years, range 11–58 years) and they were functioning at a low level on admission (mean Global Assessment Score (GAS; Endicott *et al*, 1976) 31.5 ± 22.5, range 15–90).

In summary, the probands were a primarily young, non-Hispanic white, middle to lower-middle class group of schizophrenics, who were in the early stages of the disorder.

The 725 first-degree relatives of the schizophrenic probands consisted of 9% parents, 72% siblings, and 19% children (45% male, 55% women). Specific sample sizes for different analyses depended on the definition of illness in relatives. For example, there were 713 relatives who had age information for analyses of schizophrenia and its related disorders. On average, they were 60 ± 13.7 years of age (range 17–94 years). Seventeen per cent had had no formal schooling, 43% had completed secondary education, 30% had had some tertiary education, and 9% had continued their education beyond college to graduate school.

Results

Familial risk by sex of proband and sex of relative

Figure 1 presents the cumulative hazard of onset of schizophrenia up to the age of 70 years for male and female relatives of male versus female schizophrenic probands. The hazard is estimated as the proportion of relatives affected at a particular age divided by the number of relatives unaffected by that age (Lee, 1980). There was an initial period of no risk. Then, relatives of females suffered onset of the illness more often and earlier (age 14) than relatives of males, whose risk increased in parallel from the age of 19; the risk continued to increase until the age of 47 for relatives of females, and until the age of 32 for relatives of males.

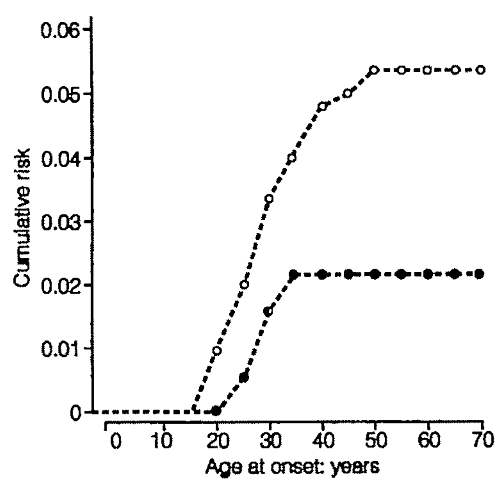

FIG. 1 Sex differences in the familial risk for schizophrenia among relatives of male (●---●) versus female probands (○---○).

The lifetime morbidity risks (Kaplan–Meier estimates) for relatives of male schizophrenic probands was 2.2% (s.e. 0.8) (7/320) versus 5.2% (s.e. 1.1) (20/393) for relatives of female schizophrenic probands ($\chi^2 = 3.9$, d.f. = 1, $P = 0.047$). This sex difference remained when we expanded the definition of illness in relatives to include schizophreniform and schizoaffective disorders: 3.6% (s.e. 1.1) of relatives of male probands were affected versus 6.3% (s.e. 1.2) of relatives of female probands ($\chi^2 = 2.8$, d.f. = 1, $P = 0.09$). These differences became significant when we examined schizophrenia, schizophreniform and schizoaffective disorders in siblings alone: 2.8% (s.e. 1.0) in siblings of male probands versus 7.9% (s.e. 1.6) in siblings of female probands ($\chi^2 = 4.90$, d.f. = 1, $P = 0.03$). However, when the definition of illness in relatives was expanded to include the full spectrum, sex differences in familial risk were attenuated: risk among relatives of female schizophrenic probands was 9.4% (s.e. 1.5) versus 8.7% (s.e. 1.7) for relatives of male probands ($\chi^2 = 0.47$, d.f. = 1, $P = 0.49$).

Survival analyses examining sex differences between male and female *relatives* with schizophrenia or spectrum disorders showed no significant differences: the risk for schizophrenia was 4.2% (s.e. 1.1) for male relatives (13/322) versus 3.6% (s.e. 0.95) for female relatives (14/391) ($\chi^2 = 0.07$, d.f. = 1, $P = 0.79$). The risk for the full spectrum in male relatives was 10.4% (s.e. 1.9) (29/322), whereas for female relatives the risk was 8.1% (s.e. 1.4) (31/394) ($\chi^2 = 0.025$, d.f. = 1, $P = 0.87$).

Finally, we examined the concordance between sex of proband and sex of affected sibling. For opposite-sex ($n = 11$) versus same-sex ($n = 10$) siblings, there was no significant difference in lifetime morbidity risk for schizophrenia: 4.4% (s.e. 1.3) versus 3.8% (s.e. 1.2), respectively ($\chi^2 = 0.13$, d.f. = 1, $P = 0.72$). In addition, although there were more female–female pairs than male–male pairs, the difference in morbidity risk was not significant: 4.7% (s.e. 1.7) versus 2.6% (s.e. 1.5) ($\chi^2 = 0.83$, d.f. = 1, $P = 0.36$).

Test for fertility effects

It was conceivable that significant sex differences in the morbidity risk for schizophrenia among relatives of schizophrenic probands could have been due to differential fertility of ill individuals in the parental generations of male versus female proband families (Risch, 1983). In order to examine this, Table I presents a test of mean differences between sibship sizes for families of female schizophrenics versus families of normal female controls, and the same comparison for male schizophrenics and male controls.

TABLE I

Comparison of sibship sizes and number of children per family for schizophrenic probands versus screened controls, controlled for sex

	Males						*Females*					
	schizophrenia (n = 171)		*controls (n = 137)*		*Wilcoxon rank sums test*		*schizophrenia (n = 161)*		*controls (n = 181)*		*Wilcoxon rank sums test*	
	mean	*s.d.*	*mean*	*s.d.*	*z*	P	*mean*	*s.d.*	*mean*	*s.d.*	*z*	P
No. of siblings per family	3.61	2.8	3.99	3.07	0.93	0.36	4.37	2.92	4.49	3.28	0.04	0.97
No. of children per family	0.50	1.08	2.69	2.16	10.52	<0.0001	1.16	1.86	3.43	2.78	8.78	<0.0001

Families from which the schizophrenic probands came were not significantly different from families of controls, whether they were from male probands ($z = 0.93$, $P = 0.36$) or female probands ($z = 0.04$, $P = 0.97$). However, female probands came from larger sibships than male probands, and this may affect sex differences in risk estimates.

In order to examine whether fertility effects were operating, sex differences in the risk of schizophrenia among children, parents, and siblings were tested separately, since it has been demonstrated that morbidity risk estimates are not affected by fertility effects for children of probands (Risch, 1983). Survival analyses demonstrated that the risk of schizophrenia among children of female probands (1.98%, s.e. 1.4, $n = 2/102$) was higher than among children of male probands (0/34), although not significantly so, as the sample size was very small. In addition, the differences remained for parents and for siblings. Thus, it was unnecessary to adjust for fertility effects in other analyses. Not surprisingly, as found in other studies (Vogel, 1979), male and female schizophrenic probands themselves were significantly less fertile than matched male and female controls (see Table I). Only 23% (40/171) of male schizophrenic probands had children as compared with 41% (66/161) of female schizophrenic probands.

Differences in the density of illness within families

Further evidence for greater risk among relatives of female probands was demonstrated in the analysis of families in which more than one person was affected versus families in which only the proband was affected.

Although 90.5% (229/253) of the schizophrenic probands were the only member of their families affected, female probands were significantly more likely than males to come from families with two or more ill members: 71% (17/24) versus only 29% (7/24) respectively ($\chi^2 = 4.18$, d.f. = 1, $P = 0.04$). There were no male schizophrenic probands who had more than one affected relative with schizophrenia, and there were three female schizophrenic probands who had more than one relative with schizophrenia. Results were similar for sibships only, when differences in sibship size between male and female probands were controlled for.

In fact, 10.6% of female schizophrenic probands had ill relatives compared with only 4.1% of males ($\chi^2 = 5.17$, d.f. = 1, $P = 0.02$). This significant sex difference was a function of two effects. First, there was a greater proportion of female probands who had a familial risk for schizophrenia, and second, among probands with at least one ill relative, the density of illness within the family was greater for female proband families controlling for sibship size.

Risk for other disorders by sex of proband

Table II presents the morbidity risks for other axis I and II disorders of male versus female probands with schizophrenia. The effect of sex on the risk for other disorders among their relatives was primarily specific for relatives with schizophrenia. Among relatives of male versus female schizophrenic probands, there were no significant differences in the risks for affective disorders, anxiety, and alcohol disorders. However, the risk for schizophrenia, schizophreniform and schizoaffective disorders combined was higher for relatives of female probands than relatives of male probands, and significantly so when siblings alone were examined. In addition, relatives of male probands had a significantly higher risk for schizotypal personality disorder than relatives of female probands ($\chi^2 = 4.1$, d.f. = 1, $P = 0.04$).

Discussion

The male *and* female relatives of female schizophrenic probands have a higher risk for schizophrenia than those of male schizophrenic probands, a finding that is not confounded by age or fertility effects. (The converse was not true: there was no significant relationship between the sex of a schizophrenic relative and sex of proband.) Further, females were more likely to come from families in which more than one person was affected, and only female probands came from families in which two or more relatives were affected.

When the definition of illness in relatives was expanded to include the full spectrum, gender differences in lifetime morbidity risk were attenuated. This was due to the inclusion of schizotypal personality disorder, for which relatives of male

TABLE II

Sex differences in lifetime morbidity risk (LTR) for other axis I and II disorders in relatives of schizophrenic probands[1]

Disorders and sex of proband	n	*LTR %*	s.e.	χ^2 *(d.f. = 1)*	P
Schizophreniform					
males	1	0.31	0.31	1.22	0.27
females	0				
Schizoaffective disorders					
males	3	1.03	0.6	0.04	0.85
females	4	1.11	0.6		
Paranoid					
males	2	0.86	0.6	0.17	0.68
females	3	1.0	0.6		
Atypical					
males	7	2.7	1.1	0.01	0.91
females	7	1.9	0.7		
Bipolar 2					
males	3	1.0	0.6	0.25	0.62
females	5	1.3	0.6		
Unipolar[2]					
males	15	6.2	1.7	1.02	0.31
females	23	11.2	4.9		
Anxiety disorders[2]					
males	11	4.3	1.3	0.025	0.62
females	11	13.1	9.2		
Alcohol disorders					
males	8	2.6	0.9	0.23	0.63
females	12	3.2	0.9		
Schizotypal personality					
males	5	1.6	0.7	4.13	0.04
females	1	0.35	0.4		
Other personality disorders					
males	0	0		1.64	0.20
females	2	0.51	0.4		
Schizophrenia, schizophreniform and schizoaffective disorders combined					
males	11	3.56	1.1	2.77	0.09
females	24	6.30	1.3		
Schizophrenia, schizophreniform and schizoaffective (siblings only)					
males	7	2.80	1.0	4.90	0.03
females	19	7.90	1.6		
All non-affective psychoses[3]					
males	17	6.1	1.5	2.1	0.15
females	30	8.0	1.4		
All affective[2] (unipolar and bipolar)					
males	18	7.2	1.8	1.30	0.25
females	28	12.4	4.9		

1. Sample consists of 399 relatives of female schizophrenic probands and 326 relatives of male schizophrenic probands.
2. All affective and anxiety diagnoses in relatives are based on Feighner criteria (Feighner *et al* 1972).
3. All non-affective psychoses = schizophrenia, schizophreniform, atypical psychoses, and paranoid disorder.

probands were at higher risk. Relatives of female probands were at higher risk for the more severe forms of the spectrum (schizophrenia, schizophreniform, and schizoaffective disorders) and relatives of males were at higher risk for the least severe form (schizotypal personality disorder). This is a curious finding, since schizophrenic women themselves have been found to have a better pre-morbid history, prognosis, and course of the disorder than schizophrenic men (Gittelman-Klein & Klein 1969; Salokangas, 1983; Goldstein, 1988). Thus, one might assume that schizophrenic women should have a lower genetic loading and lower threshold for illness that would result in higher rates of less severe forms of the illness.

It is possible that results may be explained by differential penetrance among males and females, or there may be pleiotropy, in which the pathogenic gene is less likely to be expressed as schizophrenia among men than among women. Findings in our study are equivocal with regard to testing these possibilities. On the one hand, if there was differential penetrance or pleiotropy, the expectation is that there would be different risks for schizophrenia among all men versus all women, regardless of whether they were a proband or relative. Our results showed no significant difference risk by sex of relative, and there have not been significant sex differences in prevalence reported in epidemiological studies. However, these findings remain controversial, given that previous work demonstrated a significant morbidity risk by sex of relative (Bellodi *et al*, 1986), and significant sex differences found in the course of disorder may influence prevalence estimates (Salokangas, 1983; Goldstein, 1988; Lewine, 1988).

On the other hand, given that our results showed a significantly higher risk for schizotypal personality disorder (SPD) among relatives of male compared with female probands, it may be that familial factors may be expressed as SPD in a subgroup of males, and non-familial factors may be necessary to produce schizophrenia in this subgroup. A similar hypothesis has been suggested by Mednick *et al* (1988) for schizophrenia in general. Our findings may extend Mednick's work by introducing the importance of gender in untangling the roles of familial and non-familial factors in understanding the aetiology of schizophrenia. Alternatively, the significance of our results regarding SPD may be due to a type I error, or chance, given the number of tests conducted regarding the specificity of effects and the small number of affected relatives with SPD. This would be more consistent with other findings in this study suggesting that female probands may require *more* familial factors to produce schizophrenia than males, and thus we would expect relatives of females to have a higher risk for SPD than relatives of males.

Results must be replicated in order to resolve whether sex differences in transmission reflect differential penetrance, pleiotropy, or whether there may be a sporadic form of the illness for which men are at higher risk. The overall morbidity risk for schizophrenia was low in this study (approximately 4%). Thus, there was low statistical power to find sex differences among the relatives themselves, given the effect size. However, our findings clearly demonstrated significant sex differences in the *type* of schizophrenic illness expressed among male and female relatives rather than the amount of spectrum disorders.

In addition, it is important to investigate sex differences in the mode of transmission.

Our findings are not consistent with Crow's (1988) hypothesis that the major locus of illness is in the pseudoautosomal region of the sex chromosomes, since there was not a higher same-sex concordance rate. However, in order to test his hypothesis adequately, it is necessary to examine concordance among siblings of ill mothers versus ill fathers (Crow, 1988). The study reported here could not test this.

It might be argued that the Iowa sample is not representative of all schizophrenics. However, this would not invalidate finding significant sex differences *within* the sample of schizophrenics. In order to question the validity of our results, one would have to argue that the gene pool in Iowa for females and males was different from the gene pool in other geographical areas. Given the prevailing view that schizophrenia is most likely a heterogeneous illness and that the Iowa sample was ethnically homogeneous, perhaps findings in this study are indicative of certain forms of the illness. However, our results were largely consistent with current work conducted in Italy and Japan demonstrating higher familial risk among relatives of female probands (Bellodi *et al*, 1986; Shimizu *et al*, 1987).

It might also be argued that significant sex effects are due to greater likelihood of admission if females in the sample were more severely ill and thus would have a higher genetic loading. However, this is unlikely, as female schizophrenics in this sample experienced a better pre-morbid history, later ages of onset, and better functioning on admission, suggesting that they were less severely ill. In addition, there were no significant sex differences in duration of illness before admission.

Thus, this study has demonstrated that sex is an important factor in understanding the transmission of schizophrenia, although this has not been generally reported in the literature (Wyatt *et al*, 1988). Genetic analyses should consider the importance of the sex of the proband and relative in ascertaining samples of relatives and interpreting results. At the very least, our findings underscore the importance of differential age adjustment of morbidity risk estimates by sex, given that ages of onset (and morbidity risk estimates) for schizophrenic men and women significantly differ. Finally, our results have implications for interpreting findings from high-risk studies of schizophrenia. If females are more likely to come from families with more than one schizophrenic member and, by definition, high-risk studies involve such families, then results from these studies may provide some insights into the influence of sex on the transmission of the disorder.

Sex differences in the familial transmission of schizophrenia must also be understood in light of other significant effects of sex on schizophrenia found in previous research. Perhaps, schizophrenic men with a low risk for schizophrenia have early ages of onset, poorer pre-morbid history, more deficit symptoms, more perinatal complications, and differential neurocognitive and structural brain abnormalities than schizophrenic women. They may also have a poorer response to neuroleptics and a poorer course of disorder than schizophrenic women, as has been found in previous research. Our current work has found that a number of these factors occur together and identify a subtype of schizophrenia for which men are at higher risk than women (Goldstein *et al*, 1990). Work in Britain (Murray *et al*, 1988, 1989) has also suggested that a number of these factors occur together, although they have not examined the role of sex.

Thus, sex may be an invaluable tool for delineating subtypes of schizophrenia. The significant effects of sex in schizophrenia may relate to factors inherent to being a man or woman, such as the effects of oestrogen (Seeman, 1985) and differences in brain development, or to such things as perinatal complications, for which men are at higher risk than women. In either case, sex may provide important clues to understanding the aetiological heterogeneity of schizophrenia and, perhaps, to the development of treatments that may be sex specific.

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. Beaumont G, MIMS Magazine *1988, October 15th; 67-71*

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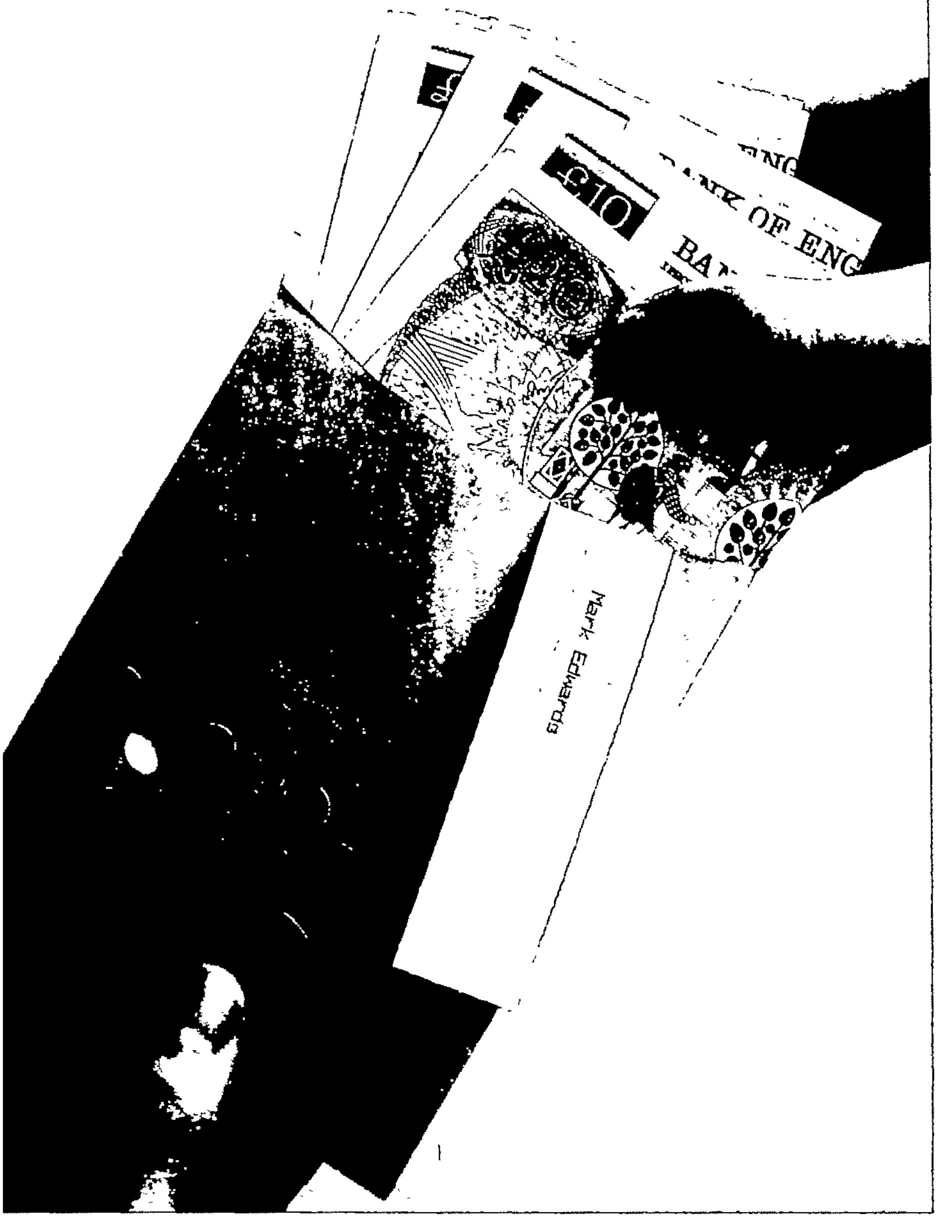

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British Journal of Psychiatry (1990), **156**, 827–834

Drug Prescribing for Schizophrenic Out-patients on Depot Injections

Repeat Surveys over 18 years

D. A. W. JOHNSON and N. F. WRIGHT

Serial surveys of the prescribing practices of psychiatrists for schizophrenic out-patients over 1970–88 showed important changes. During the interval 1970–83, polypharmacy and the use of multiple neuroleptics were reduced. The total dose of neuroleptics prescribed fell and the proportion administered by depot injection increased. Since 1983, however, some of these favourable trends have been reversed. Prescribing practices may also vary between teaching and non-teaching hospitals.

Growing concern about the harmful effects of psychotropic drugs, coupled with a wider acceptance of internal audit, has stimulated a number of surveys of prescribing for psychiatric patients (Michel & Kolakowska, 1981; Johnson, 1983*a*,*b*; Morgan & Gopalaswamy, 1984; Edwards & Kumar, 1984; Clarke & Holden, 1987; Muijen & Silverstone, 1987; Holloway, 1988). Each of these studies confirmed that both polypharmacy and inappropriate prescribing by psychiatrists are common. Comment is made that too often prescribing is frankly illogical. One survey repeated after two years observed no improvement in the drug treatments used (Clarke & Holden, 1987). A comparative study between three hospitals concluded that the presence of an academic department with a special interest in psychopharmacology resulted in more rational treatment (Muijen & Silverstone, 1987). Only Johnson (1975, 1983*a*) has specifically looked at the treatments prescribed for schizophrenic patients living in the community.

The present paper reports a series of surveys of drug treatments prescribed for schizophrenic out-patients receiving long-acting depot neuroleptic injections as part of their total treatment over the interval 1970–88. The principal results concern Manchester and Salford teaching hospitals, but a survey of non-teaching hospitals is also included.

Method

The patients for the 1970, 1975–76 and 1981–83 samples were collected by the random selection of prescription forms from Manchester and Salford hospitals. Each of these hospitals offers a comprehensive psychiatric service to a defined catchment area. All patients were on regular maintenance therapy and had been diagnosed by the treating clinical team as suffering from chronic schizophrenia. Patients were included only if they were aged 18–65 years and had been treated in the community for a minimum of six months.

The 1988 teaching-hospital sample was collected in a slightly different manner. Prescription forms were extracted on an unselective basis from the depot clinic, blind to clinical diagnosis. The clinical diagnosis and other information was then determined as before. Prescription forms were extracted until information on 100 chronic schizophrenic patients was available. In this sample each patient was then interviewed to determine the actual medication taken.

The 1985–87 sample was collected in an identical way to the 1970–83 samples, but patients were selected from non-teaching hospitals outside Greater Manchester (non-teaching sample). The sample was drawn from the main depot clinic associated with the mental hospitals, but the patients attending these clinics were determined by geographical convenience alone. The mental hospitals and associated units were offering a comprehensive psychiatric service to a defined catchment area.

All neuroleptic drug doses were converted to chlorpromazine daily mg equivalents (CPZ equivalent) using the following values:

> fluphenazine decanoate 25 mg fortnightly = flupenthixol decanoate 40 mg fortnightly = haloperidol decanoate 50 mg fortnightly = pimozide 15 mg/day = thioridazine 300 mg/day = trifluoperazine 15 mg/day = haloperidol 15 mg/day = perphenazine 12 mg/day = chlorpromazine 300 mg/day = pericyazine 300 mg/day = methotrimeprazine 150 mg/day = sulpiride 600 mg/day.

Results

In the teaching-hospital surveys there was an overall trend for polypharmacy to be reduced (Table I). This trend was greatest during the interval 1970–83; over 1983–88 the number of patients receiving two or fewer drugs actually fell marginally (72% v. 66%), with a parallel rise in the proportion of patients prescribed four or more drugs (5% v. 17%). The 1988 survey showed that only a third of schizophrenic out-patients were prescribed a single drug group for maintenance therapy, and a third of patients were prescribed three or more drug groups. The non-teaching sample showed more use of polypharmacy, with 51% on three different drug groups and 39% on four drug groups

TABLE I

Schizophrenic out-patients: drug groups prescribed to patients on maintenance depot injections (%)

	Teaching-hospital samples				*Non-teaching samples*
	1970 *(n = 140)*	*1975–76* *(n = 264)*	*1981–83* *(n = 226)*	*1988* *(n = 100)*	*1985–87* *(n = 123)*
No. of drug types prescribed					
One	0	0	28	34	1
Two	5	25	44	32	9
Three	33	18	23	17	51
Four	47	51	3	16	33
>Four	15	6	2	1	6
Neuroleptic × 1	8	56	77	63	35
Neuroleptic × 2	66	41	23	31	57
Neuroleptic × 3	27	3	0	3	8
Anti-Parkinsonian	100	98	62	48	77
Antidepressant	24	25	12	10	9
Night sedation	62	82	21	8	22
Day sedation	9	1	17	6	5
Anticonvulsant	0	0	0	0	2
Other drugs	9	10	4	4	11

or more. Only 10% of patients received two drug groups or less.

The teaching-hospital surveys reported an overall major reduction in the use of multiple neuroleptics, although over a third of patients continued to receive two or more different neuroleptic drugs after 1988 (Table I). Nearly always this was because of the use of a depot injection in combination with an oral neuroleptic of a different type. During the interval 1983–88 the trend for an increasing proportion of patients to receive a single neuroleptic was reversed (77% v. 63%).The non-teaching samples showed a greater use of multiple neuroleptic drugs, with only a third of patients prescribed a single neuroleptic drug.

There was a steady reduction in the use of anti-Parkinsonian drugs. In 1988 less than half the teaching-hospital sample were prescribed these drugs, including 5% who were allowed to use them on a flexible basis. The non-teaching sample used them more, with 77% of patients on regular prescriptions.

The use of tricyclic antidepressant drugs halved since 1970, with the frequency of use remaining stable at 9–12% for all patient samples since 1983.

The prescription of regular night sedation in the teaching-hospital samples fell steadily from 1975 (82% v. 8%). The non-teaching sample used more (22%). In all surveys the only drugs prescribed since 1975 were benzodiazepines. The use of non-neuroleptic drugs for daytime sedation was low in both samples of patients (5–6%). The only drugs used were benzodiazepines.

The use of anticonvulsant drugs and other medication was more dependent on physical status than psychiatric morbidity and has shown no meaningful change over time within the range 4–13%.

The issues of dose are more complex (Table II). In 1970 92% of patients were prescribed oral neuroleptic drugs in addition to their depot neuroleptic injections. The mean total daily dose was 1240 mg CPZ equivalents with a mean daily dose by depot injection of only 320 mg CPZ equivalents (26% of mean total daily dose). In the teaching-hospital survey of 1988 the proportion of patients on combined oral and depot injection therapy had fallen to 37%. The mean total daily dose of neuroleptics had been halved (603 mg CPZ equivalents) but the mean daily dose by depot injection had increased to 499 mg CPZ equivalents (83% of mean total daily dose). If the patients who received all their medication by depot injection are considered separately then the results show little change in the doses prescribed since 1975. The non-teaching sample had a higher

TABLE II

Mean doses (mg chlorpromazine equivalents) prescribed for schizophrenic out-patients

	Teaching-hospital samples				*Non-teaching samples*
	1970	*1975–76*	*1981–83*	*1988*	*1985–87*
Oral and depot total	1240	1184	872	603	1280
Depot injections					
all patients	320	386	363	499	343
no oral medication	305	410	420	390	386

TABLE III
Schizophrenic out-patients: dose regime of depot neuroleptic injections

Dose: mg flupenthixol decanoate equivalents	*Injection interval: days*																	
	1970 (n = 140)						*1975 (n = 264)*						*1988 (n = 100)*					
	7	*14*	*21*	*28*	*35*	*>35*	*7*	*14*	*21*	*28*	*35*	*>35*	*7*	*14*	*21*	*28*	*35*	*>35*
0–20	1	14	1	1	0	0	0	13	3	5	1	0	1	2	6	5	0	3
21–40	1	40	27	12	1	0	2	17	20	24	2	0	0	16	10	8	0	1
41–60	0	0	0	0	0	0	0	4	1	1	0	0	1	5	3	1	0	0
61–80	0	0	1	1	0	0	0	2	4	1	1	0	2	8	1	3	0	0
81–100	0	0	0	0	0	0	0	0	0	0	0	00	1	4	1	0	0	0
>100	0	0	0	0	0	0	0	0	0	0	0	0	4	11	2	1	0	0

mean total daily dose of neuroleptics, a smaller mean daily dose by depot injection (27% of mean total daily dose), but a similar mean daily depot injection dose for those receiving injections alone.

Table III analyses the use of depot injections over the 18 years surveyed. In 1970 most patients (83%) received their injections every two or three weeks. The most frequently used injection dose was 40 mg flupenthixol decanoate or equivalent (81% of patients). In 1975 the variation of dose regimes used was slightly greater. Sixty-five per cent of patients still received their injections every two or three weeks, but now 31% had injections every four weeks and 4% every five weeks. The injection doses also showed a greater flexibility. The proportion of patients on injection doses of 40 mg had fallen to 66%, those on 20 mg had risen to 22% and a new injection dose of 60 mg had been introduced (6%). A further 8% were on 80 mg each injection. In 1988 the flexibility had again increased, with a wider use of injection intervals from one week (9%) to five weeks or longer (4%). However, approximately two-thirds of patients continued to receive their injections every two or three weeks. The dose of each injection showed a much greater change. While the proportion of patients receiving the lower injection doses remained virtually unchanged, greater use was made of higher injection doses. Now 10% received 60 mg injections, 14% 61–80 mg, 6% 81–100 mg, and 18% more than 100 mg. The trend was for more patients in the middle range (60–100 mg) to receive their injections less frequently, but for a smaller group (15%) to receive not only higher injection doses but also shorter intervals between the injections.

For the 1988 teaching-hospital survey, 111 notes had to be examined to provide the required 100 patients. This suggests that over 90% of patients on long-term depot injections have a confirmed clinical diagnosis of schizophrenia. In nine patients there was a discrepancy between the hospital prescription sheets and the medication actually taken. Five patients were receiving additional medication (neuroleptics, 2 patients; antidepressants, 2 patients; benzodiazepines, 2 patients). Four patients were no longer receiving prescribed drugs (neuroleptics, 2 patients; antidepressants, 2 patients; benzodiazepines, 2 patients).

The various neuroleptics used are shown in Table IV.

TABLE IV
Neuroleptic drugs prescribed (%)

	1970	*1975–76*	*1981–83*	*1988*
Depot injections				
Fluphenazine	100	73	41	26
Flupenthixol	0	27	57	68
Clopenthixol	0	0	0	3
Haloperidol	0	0	0	2
Pipothiazine	0	0	0	1
Fluspirilene	0	0	2	0
Oral medication				
Chlorpromazine	56	26	15	17
Haloperidol	4	0	2	7
Thioridazine	12	3	2	5
Trifluoperazine	53	12	4	4
Perphenazine	20	4	0	0
Pericyazine	0	2	0	0
Methotrimeprazine	0	0	0	2
Pimozide	0	0	0	1
Sulpiride	0	0	0	1

Discussion

The serial surveys of the Manchester and Salford teaching hospitals record important changes in the prescribing practices of psychiatrists treating schizophrenic out-patients on depot neuroleptic maintenance therapy. During the interval 1970–83 polypharmacy in general, and the use of multiple neuroleptics in particular, was considerably reduced. The practice of combining oral neuroleptics with depot injections became less common and, when used, a higher proportion of the total dosage was administered by injection. The total dose of neuroleptics received by individual patients was significantly reduced. The surveys showed also that the use of depot injections became progressively more flexible, with a wider variation in both the injection dose and the interval between injections, to meet the personal needs of the individual patient. A substantial reduction in anti-Parkinsonian drugs, tricyclic antidepressants and benzodiazepines was also noted.

However, during the interval 1983–88 less desirable changes were evident. Although the general trend for reduced polypharmacy continued, the use of neuroleptic drugs showed a reversal of some previous trends. An increased proportion of patients received two or more neuroleptics (34% v. 23%) with more than a threefold increase in the proportion of patients receiving four or more different drugs (17% v. 5%). In particular, the practice of combining a depot injection with an oral neuroleptic of a different type increased considerably.

There is now general agreement that, with the possible exception of the early weeks of treatment, patients should be prescribed anti-Parkinsonian drugs as part of maintenance only when a need has been demonstrated. There is no place for the long-term routine prescriptions of anticholinergic drugs (Johnson, 1988*a*). Surveys of extrapyramidal side-effects report wide variations in their prevalence (10–88%) and this is probably partly because these side-effects are dose-dependent at normal clinical levels. A further complication is that few studies record essential dependent variables, which makes interpretation of the results difficult. One study demonstrated that over half of these side-effects could be abolished by dose reductions without loss of therapeutic control (Johnson, 1973). A further prospective study of side-effects over 15 months reported a prevalence rate of 81%, but demonstrated that when morbidity was plotted over time, an early high morbidity fell to a stable level of 15–24% after four to five months in the community (Johnson, 1978).

These results emphasise the need to reassess the use of anti-Parkinsonian drugs. McClelland *et al* (1974) reviewed the literature on the discontinuation of anticholinergic drugs in schizophrenic patients receiving regular neuroleptic medication. Only a minority of patients (4–27%) developed extrapyramidal symptoms on stopping these drugs. Johnson (1978) reported a recurrence of symptoms in 10%. Rifkin *et al* (1978) in a different literature search reported a reappearance of symptoms in 9–43% of patients. Jellinek *et al* (1981) reported the highest number of patients developing new symptoms on stopping anticholinergic drugs (62%).

Although the emphasis of these surveys may vary, the general conclusion is the same. Not all patients prescribed anticholinergic drugs in the presence of extrapyramidal symptoms need to continue on these drugs long term. Since at any one time approximately 60% of patients on maintenance therapy are prescribed these drugs, the above results suggest that no more than 25–30% of patients actually need them.

It must not be forgotten that the classic extrapyramidal symptoms are not the only indication for the use of anticholinergic drugs. The akinetic syndrome (akinetic depression) rapidly responds to these drugs (Rifkin *et al*, 1975; Van Putten & May, 1978). Johnson (1981) estimated that 10–15% of all 'depressive' symptoms in schizophrenia were due to this syndrome.

The anticholinergic drugs have their own range of important side-effects. Reviews of the literature (Johnson, 1982, 1984) show that some of these unwanted effects are similar to the neuroleptic effects under treatment. Moreover, they may reduce the therapeutic effects of the neuroleptic drugs or cause a toxic psychosis, although the mechanism of action is not clear (Simpson *et al*, 1980; Johnstone *et al*, 1983).

The issues surrounding the prescription of antidepressants are more complex and the solutions less clear. The importance of depression in the life of a schizophrenic patient has only recently been researched in depth, despite it being one of the most common symptoms experienced by patients (Cheadle *et al*, 1978). The aetiology is complex and it is unlikely that a single cause is responsible for all depression, even in an individual patient (Johnson, 1986). There is very little information in the literature to support the use of antidepressants in these patients. Simpson *et al* (1972) showed a significant deterioration in schizophrenic patients treated with tricyclic antidepressants alone. Prussoff *et al* (1979) combined amitriptyline and perphenazine in maintenance treatment: over four months there was a reduction of depressive symptoms although the final analysis showed no overall advantage for the combination therapy. The addition of amitriptyline caused a high drop-out rate in the first month due to increased thought disorder. Only two double-blind placebo-controlled trials have explored the response of new depressive symptoms to the addition of a tricyclic antidepressant to existing neuroleptic drug therapy. Johnson (1981) failed to identify any therapeutic benefit from the addition of nortriptyline in stable schizophrenic out-patients who had lived in the community for more than one year since discharge. Siris *et al* (1987) demonstrated a positive response to the addition of imipramine in patients with post-psychotic depression. It is clear that at the present time the prescription of antidepressants must be regarded as a therapeutic trial. Since there are possible risks of a schizophrenic deterioration these patients must receive careful supervision.

The benzodiazepine drugs were prescribed principally for night sedation. It is known that these drugs have no antipsychotic or antidepressant effect (Johnson, 1983*b*). An awareness of the risks of rapid addiction has led to a major reduction in the use of benzodiazepines in general. Their use in a vulnerable population such as schizophrenic patients, except for short-term interventions, is particularly harmful. The pattern of prescribing in these surveys appears to recognise these hazards.

It is difficult to understand the logic of combining different conventional or 'typical' neuroleptics since they do not differ appreciably in their therapeutic effects. However, their other properties, such as the blocking effects of adrenergic, cholinergic, histaminergic, or serotonergic receptors, can vary and may explain the differing side-effects (Stahl & Wets, 1988). To combine different neuroleptics is to risk a wider spectrum of side-effects without any potential for improved therapeutic response.

The desirability of having a personalised, flexible and usually reducing dose in maintenance neuroleptic therapy has now been established. Johnson (1973) demonstrated that, with the depot injection, the extrapyramidal side-effects produced were dependent on dose within the usual clinical dose range. Two-thirds of these side-effects were abolished by a dose adjustment without loss of therapeutic control over a 15-month follow-up. A reanalysis of this study together with a second study (Johnson, 1975) concluded that after six months in the community nearly half the patients could have their maintenance dose significantly reduced. After 12 months from hospital discharge it was estimated that two-thirds of patients who had survived free of relapse required no more than half their dose at the time of discharge. Chien (1975) reported that out-patients allowed to regulate their own prescriptions, resulting in a reduced dosage, had an equal survival rate as patients maintained on physician-determined doses, and Hogarty *et al* (1976) observed that in stabilised out-patients there was little difference in relapse rates on varying dose prescriptions; neither of these authors comment on whether any of the prescriptions used were appropriate.

The crucial observation that probably did most to stimulate research on dose levels and alternative treatment strategies was the review of all controlled trials that permitted estimates of the equivalent dose of chlorpromazine to be plotted against relapse, by Baldessarini & Davis (1980). The found no significant dose-effect between 100 and 2000 mg/day, and no difference in outcome at doses above and below 310 mg/day. In an open study Capstick (1980) showed that some chronic schizophrenic patients could be successfully maintained on very small doses (6.25–12.5 mg fluphenazine decanoate every eight weeks). This study also suggested that in the phase of very low dose the environmental factors became more relevant to relapse because of a reduced buffer effect. This view is supported by both Hogarty (1984) and Leff *et al* (1984).

The possibility that very high doses may increase the therapeutic effect, particularly among patients resistant to standard neuroleptic doses, has been investigated by a number of authors (Rifkin *et al*, 1971; Quitkin *et al*, 1975; McClelland *et al*, 1976; Dencker *et al*, 1978; McCreadie *et al* 1979). The consensus view is that very high doses have not proved beneficial. McCreadie *et al* (1979) suggested that very high doses might be useful if only for patients who fail to achieve reasonable plasma levels with standard doses, but so far this hypothesis has not been fully explored. Johnstone *et al* (1983) and Smith *et al* (1984) demonstrated a curvilinear response, with an increase beyond a critical threshold reversing the therapeutic gain of the lower dose. Other authors (Curry *et al*, 1970; Van Putten, 1974; Simpson *et al*, 1976) have reported exacerbations of psychotic symptoms on high doses which improve with a dose reduction.

Animal studies show differences for the 'typical' and 'atypical' neuroleptics. With 'typical' neuroleptics the antipsychotic (hyperactivity) action occurs at a similar dose level to its catalepsy (extrapyramidal) effect. With the 'atypical' neuroleptics the antipsychotic effect may occur at a much lower level (Stahl & Wets, 1988).

So far six double-blind trials have attempted to compare the effects of very low doses and standard doses. The study by Lehmann *et al* (1983) breached randomisation procedures, resulting in significant differences in the patient groups compared. A Birmingham study (unpublished) of newly discharged in-patients had to be abandoned on ethical grounds because of high relapse rates. Four studies have been completed successfully (Kane *et al*, 1983; Marder *et al*, 1984, 1987; Johnson *et al*, 1987; Hogarty *et al*, 1988), but it is important to recognise that no individual study, nor indeed the studies collectively, allows us to make a final recommendation on the use of very low doses, as the samples and regimes studied varied enormously.

Despite their differences all these studies demonstrate that if patients are randomly allocated to low-dose prescriptions there is an increased risk of deterioration or relapse, although not necessarily requiring in-patient treatment. Not all patients suffer deterioration, and for selected patients this might be a most advantageous treatment strategy if we succeed in identifying the correct patients. The risk of relapse is minimised by the use of flexible-dose schedules, and many minor relapses may respond to an increased dose without serious consequences if the patient is under careful supervision. Short-term evaluations may be misleading in evaluating the risk:benefit ratio: it was disappointing to note that although the early risks of extrapyramidal side-effects may be reduced, no differences were recorded after 12 months.

A recently suggested strategy is that of 'targeted intervention'. Herz & Melville (1980) reported that prodromal changes are frequently noticed by either the patients (70%) or families (92%), with agreement in 66% of cases. The non-specific changes reported are those of tension, anxiety, mood changes, a change of sleep pattern, and a loss of appetite. Johnson (1988*b*) reported depression as the most common symptom preceding psychotic relapse and identified this change as relevant in the prediction of relapse. It was noticed by either patients or relatives before 30–40% of relapses. Two pilot studies comparing regular maintenance medication with targeted intervention in response to prodromal changes in patients on no regular medication reported encouraging results (Herz *et al*, 1982; Carpenter *et al*, 1987). In a much larger study Jolley *et al* (1989) found that brief intermittent treatment over one year was associated with a significantly higher rate of psychotic, neurotic, and dysphoric symptoms when compared with maintenance antipsychotic medication. However, intermittent treatment may have some favourable impact in reducing the risk of tardive dyskinesia. It would be valuable to explore the application of a 'targeted intervention' in patients on very low doses compared with those receiving no regular medication or standard-dose therapies. It may also be useful as a challenge strategy in patients considered for discontinuation. However, to achieve the outcomes reported, regular patient contact on a weekly or two-weekly basis is required.

Every effort must be made to monitor patients carefully on personalised, flexible-dose regimes. The normal expectation should be for patients to have carefully supervised dose reductions over time. More research is required, but present research clearly indicates that for chronic schizophrenia maintenance therapy in excess of five years is required because of the continuing risk of relapse in 80% of patients.

The 1988 survey indicates that clinicians must regularly check the understanding patients have of their prescriptions. Nine per cent were taking medication different from that prescribed by the treating psychiatrist.

Although both the teaching-hospital samples and the non-teaching samples were obtained from hospitals offering a comprehensive service to a defined catchment area, great caution must be used in making any direct comparison. The results from the non-teaching hospitals were included primarily as a source of additional information since these supported all the findings from the Manchester and Salford hospitals. However, it is reasonable to observe that in these hospitals, polypharmacy is an even greater problem. In particular the use of several neuroleptics was high, with a frequent combination of depot injections and oral medication. The total dose of neuroleptic drug was higher and the proportion administered by depot injection lower. The use of anti-Parkinsonian drugs and benzodiazepines was also higher. These trends add support to the conclusions of Muijen & Silverstone (1987).

These surveys clearly suggest that although the drug treatment of chronic schizophrenia in the community has improved significantly over the past 18 years, there remain important areas of concern. Drug prescriptions remain far from optimal. Perhaps the area of greatest concern is the suggested deterioration in drug-prescribing practices in a major teaching centre involved in psychopharmacological research. It is unlikely to be a problem occurring on an isolated basis. It stresses the need for regular internal audits and constant vigilance in supervising the depot injection clinics. It has always been the view of one author (DAWJ) that all patients attending these clinics should remain under consultant supervision, continuing to attend the normal outpatient clinics. The depot injection of neuroleptics should not be regarded as an easy alternative, with patients relegated to a 'production line' method of care. Depot injection clinics should act as the fulcrum for an improved and more carefully monitored management programme. This must include a regular review of the patient and the prescriptions offered.

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Problems Reported by Relatives in a Community Study of Dementia

D. W. O'CONNOR, P. A. POLLITT, M. ROTH, C. P. B. BROOK and B. B. REISS

The supporters of 120 demented elderly people completed rating scales of the frequency and severity of the problems they faced, the amount of strain they experienced and their psychological well-being. Problems and strain increased with the degree of dementia. Problems relating to physical dependency, forgetfulness and inertia were relatively common, while disturbed behaviours were relatively uncommon. Physical dependency and disturbed behaviour were less well tolerated than forgetfulness and inertia, but all problem categories were positively associated with measures of strain. Wives reported more problems and strain than husbands, and co-resident children were under greater strain than children who lived independently.

Community services will succeed in helping demented elderly people remain in their own homes only if the assistance they offer genuinely meets the needs of the family members who support them (O'Connor *et al*, 1989*a*). There is good evidence that early, practical intervention reduces the numbers of frail elderly people admitted to residential homes (Challis & Davies, 1986) but we have little information about which aspects of dementia create the greatest difficulty for relatives, the vast majority of whom will never be referred to specialist centres (O'Connor *et al*, 1988).

In a recent community survey, Eagles *et al* (1987*a*,*b*) found that the stress reported by relatives escalated as dementia advanced and that relatives who lived with a demented spouse or parent reported greater stress than those who lived separately. In addition, measures of stress correlated positively with the degree of disturbed and dependent behaviour exhibited by demented subjects.

We report here on the problems faced by the supporters of demented people identified in a survey of the prevalence of dementia in Cambridge. In particular, we examine the frequency and severity of problems associated with dementia, and the relationship between the problems reported by relatives and the level of strain they experienced.

Method

Survey design

The methods employed in this study have been described in detail elsewhere (O'Connor *et al*, 1989*b*). In brief, the names of all patients aged 75 years and over were taken from the age-sex registers of six Cambridge general practices together with a one in three sample of names from a seventh practice to make up the numbers required for a later part of the project. Only patients who were living at home or in sheltered accommodation are considered here.

Patients were screened for cognitive impairment using the Mini-Mental State Examination (Folstein *et al*, 1975) and those who scored 23 or below out of a maximum score of 30, together with a one in three sample of those scoring 24 and 25, were selected for more intensive investigation using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth *et al*, 1986).

The CAMDEX is a structured diagnostic interview schedule designed for use in community studies of dementia. It comprises a mental-state examination, a medical and psychiatric history, detailed cognitive testing and an interview with an informant (in this case, the patient's supporter), to determine whether there has been any deterioration in subjects' intellect, personality, behaviour or mood. Operational criteria for diagnosing dementia, virtually identical to DSM–III criteria (American Psychiatric Association, 1980), and descriptive criteria for rating dementia severity are appended to the schedule.

Rating scales

Wherever possible, the informant was the family member most frequently in contact with the elderly subject. If no family member was available, a friend, neighbour or home help was interviewed instead, but only the reports provided by relatives are included in this paper. Supporters were asked to complete a rating scale of the frequency and severity of 34 abnormal behaviours commonly associated with dementia (Gilleard, 1984). Behaviours were rated as occurring 'never' (zero points), 'occasionally' (one point) or 'frequently' (two points). Scores were summed to produce a 'problem frequency score' with a maximum score of 68 points. If behaviours arose at least occasionally, they were rated by supporters as causing 'no problem' (zero points), a 'small problem' (one point) or 'a big problem' (two points). Scores were summed to produce a 'problem severity score' with a maximum score of 68 points again. For the purposes of this paper, items were grouped into three categories, namely physical dependency (13 items), disturbed behaviour (11 items) and forgetfulness-inertia (10 items) and problem frequency and severity subscores were computed for each category.

Supporters also completed a rating scale of strain which inquired into feelings of frustration, anxiety and depression, disturbed sleep, lack of holidays and financial difficulties (Gilleard, 1984). Items were coded as arising 'never' (zero points), 'sometimes' (one point) or 'often' (two points) with a maximum score of 26 points. Finally, supporters completed the 28-item version of the General Health Questionnaire (GHQ–28) (Goldberg & Hillier, 1979) which measures symptoms of anxiety, depression, somatic disturbance and social dysfunction.

Study population

Problem and strain scales were obtained for 120 of the 145 demented elderly people who were living at home or in sheltered accommodation with the support of a family member. Two subjects would not allow us to interview their relatives and data are missing for 23 supporters who lived too far away to be interviewed in person.

Fifty-eight subjects were mildly demented, 50 were moderately demented and 12 were severely demented. The ages of the 42 men and 78 women ranged from 75 to 106 with a mean of 83.9 years. Twenty-four had been assessed previously by the psychogeriatric service (2 mild, 11 moderate, 11 severe); none attended the psychogeriatric day centre and only four had been admitted for assessment or family relief (one moderate, three severe). Their supporters included 43 spouses, 50 children (18 co-resident) and 27 other relatives including siblings, nieces, nephews and grandchildren (seven co-resident).

Community-resident elderly people who were found using the CAMDEX to be cognitively intact provided baseline measures of problem frequency, problem severity and supporter strain. Rating scales were available in 107 of 151 cases. Data are missing for another 44 supporters. The normal subjects' mean age was 82.0 with a range of 75 to 97 years. A proportion were frail and physically disabled; 26 could walk no further than the front gate, 39 needed help with shopping and 42 could manage only light housework.

Results

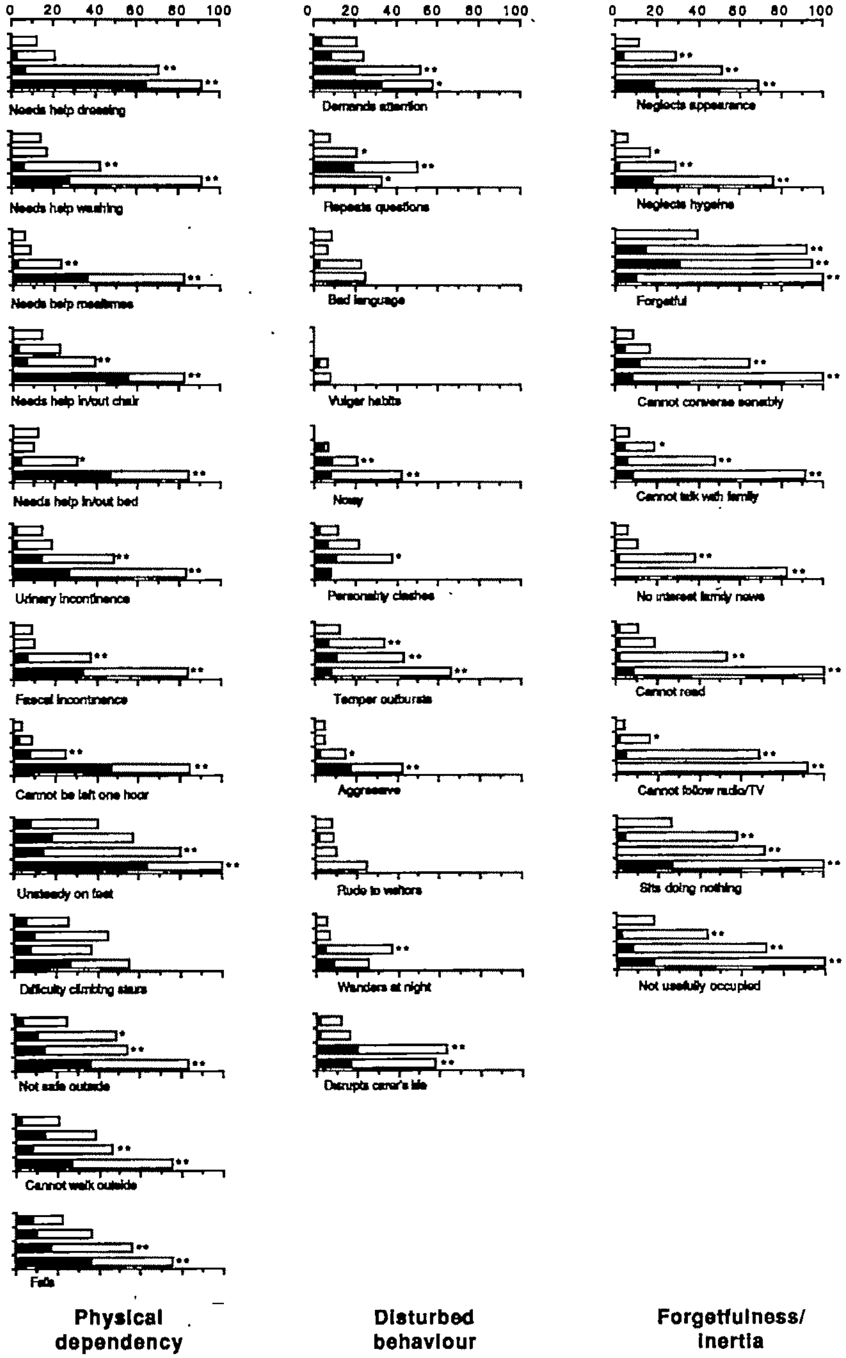
Table I lists the rating scale scores given by the supporters of normal, mildly, moderately and severely demented subjects. The supporters of demented subjects reported a larger number of problems, greater problem severity and greater strain, and their scores increased in line with the advance of dementia; only the GHQ-28 failed to detect statistically significant differences between the normal and demented groups. Demented subjects were frequently rated as being physically dependent, forgetful and inert. By contrast, disturbed behaviours arose much less commonly. Physical dependency items were rated as causing major problems more commonly than disturbed behaviours or forgetfulness and inertia but these findings make greater

TABLE I

Mean scores (and standard deviations) on problem frequency, problem severity, strain and GHQ-28 rating scales

Rating scale	*Normal (n = 107) Mean (s.d.)*	*Mild dementia (n = 58) Mean (s.d.)*	*Moderate dementia (n = 50) Mean (s.d.)*	*Severe dementia (n = 12) Mean (s.d.)*	*Combined dementia (n = 120) Mean (s.d.)*	*Maximum score*	*Paired t-tests (combined dementia cases)*
Problem frequency							
(A) physical	3.2	5.2**	9.2**	18.7**	10.5**	26	A v. B, t = 11.94, $P<0.005$
dependency	(5.0)	(5.8)	(7.1)	(5.6)	(8.1)		
							A v. C, t = 1.66, $P=0.099$
(B) disturbed	1.0	1.8**	4.5**	4.9**	3.5**	22	
behaviour	(2.1)	(2.3)	(4.0)	(4.0)	(3.9)		B v. C, t = 13.85, $P<0.005$
(C) inertia-	1.8	4.88*	10.1**	15.9**	9.8**	20	
forgetfulness	(2.8)	(3.5)	(5.2)	(3.1)	(6.1)		
Problem severity							
(A) physical	2.4	3.3	5.0**	13.3**	5.1**	26	A v. B, t = 3.97, $P<0.0005$
dependency	(3.0)	(3.8)	(5.0)	(6.3)	(5.3)		
							A v. C, t = 4.97, $P<0.0005$
(B) disturbed	1.8	2.0*	3.8*	3.8	3.3*	22	
behaviour	(2.0)	(2.4)	(3.8)	(4.2)	(3.6)		B v. C, t = 0.93, $P<0.357$
(C) inertia-	0.9	1.6	3.3**	4.8**	2.5**	20	
forgetfulness	(1.8)	(2.3)	(3.0)	(3.8)	(2.9)		
Strain	4.3	7.0**	10.3**	11.4**	9.1**	26	
	(4.8)	(5.2)	(5.2)	(5.8)			
GHQ-28	2.4	3.2	3.4	2.6	3.1	28	
	(3.9)	(4.8)	(4.3)	(5.3)			

*$P<0.05$, **$P<0.01$ (Mann-Whitney U-test, normal v. mild, moderate, severe and combined dementia).



Problem frequency scores, demented v. normals, Pearson's X, (1 d.f.) $^{*}P<0.01$, $^{**}P<0.001$.

FIG. 1. Proportions of supporters who rated behaviours as occurring occasionally or frequently (white + black bars) and the proportions who rated behaviours as a severe problem (black bars). Scores for normal, mildly, moderately and severely demented subjects are shown in descending order.

sense when problem severity is related to problem frequency (see below).

Figure 1 shows (a) the proportions of the supporters of normal and demented subjects who rated particular behaviours as occurring occasionally or frequently and (b) the proportions who rated behaviours as causing severe problems. The figure can be analysed in the following way. Taking 'needs help with dressing' as an example (column one, item one), 92% (black + white bar) of those with severely demented relatives (bottom bar) provided help with dressing at least occasionally and 64% (black bar only) rated dressing as a major problem. Put another way, 70% (64/92) of those who were required to provide help at least occasionally rated dressing as posing severe difficulties. This last figure adjusts for differences in the frequency of individual behaviours and gives a rough measure of supporters' level of tolerance. For this reason, the proportion of supporters reporting that a behaviour occurred at least occasionally who rated it as a severe problem will be called the 'tolerance ratio'.

Mildly demented elderly people achieved significantly higher problem frequency ratings than the normal controls on only a few items including repeating questions, temper outbursts, lack of concern for appearance and hygiene, forgetfulness and measures of apathy (e.g. sits doing nothing). By contrast, there were highly statistically significant differences between controls and moderately and severely demented subjects on virtually every item.

Although the supporters of severely demented elderly people rated many of the physical dependency items as posing frequent problems, most behaviours were remarkably well tolerated. For example, 82% of the severely demented subjects were incontinent of urine at least occasionally but only 23% of their supporters (or 28% of those affected) saw wetting as a major problem. The five least tolerated behaviours, taking all cases of dementia together, were demands for attention ('tolerance ratio' 41%), 'cannot be left one hour' (41%), noisiness (40%), falls (30%) and personality clashes (30%). The five best tolerated behaviours were lack of interest in family news (3%), 'sits doing nothing' (6%), 'cannot read' (7%), rudeness to visitors (9%) and 'not usefully

TABLE II

Mean rating-scale scores (and standard deviations) of spouses, co-resident and non-resident children caring for demented subjects

Severity of dementia	*Spouses (S) Mean (s.d.)*	*Co-resident children (CRC) Mean (s.d.)*	*Non-resident children (NRC) Mean (s.d.)*	*Mann–Whitney significance values**
Mild dementia	($n=18$)	($n=7$)	($n=19$)	
problem frequency	10.1	15.6	10.7	
	(7.2)	(10.1)	(8.0)	
problem severity	3.3	9.1	5.0	
	(4.8)	(8.3)	(6.2)	
strain	5.5	13.0	6.9	S v. CRC, $P=0.013$
	(4.9)	(5.5)	(4.4)	CRC v. NRC, $P=0.024$
GHQ-28	2.8	5.5	3.8	
	(4.1)	(5.5)	(6.2)	
Moderate dementia	($n=19$)	($n=9$)	($n=11$)	
problem frequency	24.1	31.2	17.6	CRC v. NRC, $P=0.013$
	(12.7)	(8.3)	(10.2)	
problem severity	11.0	14.7	7.9	
	(7.7)	(8.8)	(8.4)	
strain	9.9	14.2	9.9	CRC v. S, $P=0.057$
	(5.3)	(4.4)	(4.4)	CRC v. NRC, $P=0.084$
GHQ-28	4.9	3.4	2.9	
	(4.5)	(4.7)	(4.3)	
Severe dementia	($n=6$)	($n=2$)	($n=2$)	
problem frequency	38.5	47.5	39.5	not tested[1]
	(7.1)	(2.1)	(10.6)	
problem severity	19.5	27.0	33.5	
	(8.3)	(7.1)	(12.0)	not tested[1]
strain	10.8	11.5	16.5	
	(4.4)	(10.6)	(3.5)	not tested[1]
	(4.4)	(10.6)	(3.5)	
GHQ-28	1.2	2.0	9.0	
	(1.3)	(2.8)	(12.7)	

*Values listed only if $P<0.1$.

1. Not enough cases to permit statistical analysis.

occupied' (10%). The mean 'tolerance ratios' for all cases of dementia were 25.5% for physical dependency items, 19.8% for disturbed behaviour items and 10.9% for forgetfulness-inertia items.

Strain scores, including those for cognitively intact subjects, correlated strongly with total problem frequency scores and total problem severity scores. Pearson correlation coefficients were +0.670 ($P<0.0005$) and +0.712 ($P<0.0005$) respectively. Correlation coefficients between strain scores and physical dependency, disturbed behaviour, and forgetfulness-inertia *frequency* subscores were +0.545, +0.580 and +0.318 respectively while the correlation coefficients between strain scores and physical dependency, disturbed behaviour and forgetfulness-inertia *severity* subscores were +0.539, +0.612 and +0.484 respectively. All of these coefficients were highly statistically significant ($P<0.0005$).

The rating-scale scores of spouses, co-resident and non-resident children are compared in Table II. Co-resident children cared for a smaller proportion of moderately and severely demented subjects than spouses and non-resident children but, even when dementia severity is held constant, they reported greater problem frequency and severity, and experienced more strain, than the latter two groups. Co-resident children caring for mildly demented relatives had significantly higher strain scores than either spouses or non-resident children while co-resident children caring for moderately demented relatives reported significantly more problems than spouses and appeared to experience more strain than both spouses and non-resident children. There were no significant differences on any of the scales between spouses, who were all co-resident, and children who lived in separate households. There were too few severely demented cases to permit statistical analysis.

The scores given by husbands and wives are compared in Table III. Husbands and wives caring for mildly demented spouses did not differ significantly on any of the scales used. However, wives caring for moderately demented husbands showed a tendency to report more problems, experience greater strain and have higher GHQ-28 scores than their male counterparts. We found no substantial evidence that wives were excessively burdened because of a greater reluctance to admit their spouses into care; 21% (15/55) of the demented men identified in the survey lived in institutions compared with 30% (49/116) of the demented women ($\chi^2=1.696$, 1 d.f., $P=0.193$). Certainly, we found more wives supporting demented husbands than husbands supporting dementing wives, but the reason for this discrepancy very probably lies in the greater longevity of women. Because women live longer than men, a higher proportion will have lost their spouses before the onset of their dementia.

Demented men, including those cared for by wives, children and other relatives, were rated as needing more help than demented women on several of the physical dependency items. For example, 60% of all demented men were said to need help with dressing compared with 32% of the women ($\chi^2=7.384$, 2 d.f. $P=0.007$); 48% needed help to wash compared with 27% of women ($\chi^2=4.319$, 2 d.f., $P=0.037$) and 38% needed help getting in or out of bed compared with 19% of women ($\chi^2=4.134$, 2 d.f., $P=0.042$). Women were rated as causing more problems than men on only a few items, namely demanding attention, creating personality clashes and asking questions repeatedly, but none of these differences were statistically significant.

The strain scale included the question, 'Do you get any satisfaction from caring for your relative?' Five (5%) of those supporting normal elderly relatives said that they derived no satisfaction from their role, compared with four (7%) and 10 (20%) of those supporting mildly and moderately demented relatives respectively ($\chi^2=12.53$, 6 d.f., $P=0.051$). Although five (42%) of those caring for severely demented elderly people said that they derived satisfaction only occasionally from their task, none said that they gained no satisfaction at all. Overall, there were no differences in the answers given by husbands and wives and none between those caring for male and female relatives. Co-resident children with demented parents gained least satisfaction: four (22%) gained no satisfaction at all, compared with six (13%) of the spouses and three (9%) of the non-resident children ($\chi^2=6.63$, 4 d.f., $P=0.157$).

TABLE III

Mean rating-scale scores (and standard deviations) of husbands and wives caring for demented spouses

Severity of dementia	*Husband caring for wife*	*Wife caring for husband*	*Mann–Whitney significance values**
	Mean (s.d.)	*Mean (s.d.)*	*Mean (s.d.)*
Mild dementia	($n=5$)	($n=13$)	
problem frequency	8.2	10.8	
	(10.2)	(6.1)	
problem severity	4.2	3.0	
	(7.8)	(3.3)	
strain	6.2	5.2	
	(8.4)	(3.0)	
GHQ-28	2.8	2.8	
	(5.7)	(3.4)	
Moderate dementia	($n=8$)	($n=11$)	
problem frequency	17.8	28.6	$P=0.065$
	(11.7)	(11.8)	
problem severity	10.2	11.5	
	(9.4)	(6.6)	
strain	7.0	12.3	$P=0.031$
	(4.8)	(4.5)	
GHQ-28	2.9	6.8	$P=0.067$
	(2.9)	(5.0)	
Severe dementia	($n=2$)	($n=4$)	
problem frequency	36.0	39.8	not tested[1]
	(12.7)	(4.9)	
problem severity	20.5	19.0	not tested[1]
	(13.4)	(7.3)	
strain	13.5	9.5	not tested[1]
	(3.5)	(4.7)	
GHQ-28	0.0	1.8	not tested[1]
	(0.0)	(1.3)	

*Values listed only if $P<0.1$.

1. Not enough data for statistical analysis.

Discussion

The problems which supporters find most difficult to bear will vary from one survey to another because of differences in study locale and in the instruments used to measure problem frequency and severity. In hospital studies, the most onerous difficulties have been variously described as sleep disturbance, faecal incontinence and immobility (Sanford, 1975); passive, withdrawn behaviour and disturbed mood (Greene *et al*, 1982); demands for attention (Gilleard *et al*, 1982); and abusiveness, inappropriate micturition and faecal smearing (Argyle *et al*, 1985).

In this community population, physical dependence caused frequent problems of a relatively high degree of severity; disturbed behaviours occurred less frequently but were tolerated almost as poorly; and items relating to apathy and inertia were generally well tolerated despite being very common indeed. Even so, all three categories were significantly and positively associated with measures of strain, perhaps because behaviours rarely arise independently. Most confused, apathetic demented people will also require help with everyday activities and a proportion will also create disturbances from time to time. From a practical point of view, our findings underline the importance of the help and advice already provided by community nurses, occupational therapists and physiotherapists in the areas of bathing, dressing and mobility. Disturbed behaviours are much less easily remedied but publications like *The 36-Hour Day* (Mace & Rabins, 1985), which offer simple, clear advice about how to deal with wandering, repeated questioning and sleep disturbance, are much appreciated by family members and should be made readily available.

Although one-fifth of our moderately demented subjects had been assessed by psychiatrists, none attended the local psychogeriatric day unit. Consequently, we expected to find that they posed fewer problems than patients described in previous day hospital studies. This proved not to be the case. Gilleard *et al* (1984) administered an identical problem checklist and strain scale to the supporters of demented elderly people attending an Edinburgh psychogeriatric day hospital. We chose to compare these patients with our moderately demented group on the grounds that few of our mildly demented subjects warranted day hospital care, while all of our severely demented subjects were too profoundly disabled to be cared for in this sort of setting.

Similar proportions in the Edinburgh and Cambridge groups required help with physical care, were forgetful and lacked interest and drive. However, the proportions of supporters who rated problems as being severe were markedly different. For example, while 57% of the Edinburgh patients needed help to dress compared with 54% in our moderately demented group, dressing was rated as a major problem by 35% of the day hospital supporters compared with only 6% in Cambridge. Similarly, 61% of the day hospital patients were said to disrupt their supporters' lives compared with 63% in Cambridge. While 42% of the Edinburgh supporters rated this as a serious problem, only 20% of Cambridge supporters did so. The comparison is crude but our findings suggest that supporters' tolerance levels play a critical part in determining whether or not elderly people are referred for specialist assessment.

'Problem severity' and 'strain' are subjective measures and naturally some supporters will find the going harder than others. In our study, the wives of moderately demented men reported more problems and greater strain than husbands, even though demented men in Cambridge were no more likely than women to suffer from disorders such as strokes or Parkinson's disease which lead to greater than usual physical dependence (O'Connor *et al*, 1989*b*). One explanation is that women find the sheer physical effort involved in dressing, lifting and toileting more taxing than men. In addition, Gilhooly (1984) speculated that male supporters find it easier to go out, leaving their dependent spouses unattended. If this is the case, the break they get from caring might influence their perception of the difficulties they face.

We formed the strong impression that women take on the role of 'nurse' earlier than men, perhaps because their husbands expect them to do so. Many of the husbands in our study enjoyed being 'carers' and took great pride in their new-found accomplishments. For them, caring gave meaning and direction to their lives, in contrast to many of the wives who saw their role as burdensome. Admittedly, equal proportions of husbands and wives reported that they gained satisfaction from their work but the possibility remains that the latter find it easier to admit to 'problems' and 'strain' than to 'dissatisfaction' which might be interpreted as a sign of disloyalty. Our findings suggest that wives might benefit from being encouraged to allow their husbands to retain as much independence as possible, even if this leads to untidiness and inefficiency. Support groups, which many relatives find helpful, might be an ideal forum for this sort of discussion.

Gilleard *et al* (1984) found that children and children-in-law reported greater strain than spouses. In our study, the supporters under greatest strain were children living with a demented parent.

Children who shared their home with a spouse, children of their own, and a demented mother or father faced a multitude of problems from which they had little or no escape, while many of the single or widowed children who lived alone with a demented parent led bleak and lonely lives. Since most of these sons and daughters were able-bodied, services like home helps and meals-on-wheels hardly applied. Instead, day care and relief admissions might be of particular benefit to this group.

Despite the burden imposed on supporters, the majority continued to derive satisfaction from their role and few achieved high scores on a rating scale of psychological ill-health. However, it is important to note that relatives who were completely unable to cope might have relinquished care and been lost to the study. Some supporters, by dint of temperament, ill-health or conflicting responsibilities, will find caring for a demented relative unusually difficult and withdraw at an early stage while others will choose to persist beyond the call of duty. The supporters of our severely demented subjects, all of whom had refused offers of institutional care, reported not much more strain that those caring for moderately demented subjects. This highly select group generally offer a much higher standard of care than insitutions and at a lower cost to the community. As a result, they clearly warrant the greatest possible efforts on the part of the social and psychiatric services to support them in their task for as long as possible.

Predicting which cases will benefit from intensive community care, and which cases would be better admitted into residential homes without further ado, will doubtless prove difficult because of the large number of variables which need to be taken into account, but the task is important if services are to be effectively and sensibly distributed (Opit, 1977). In one day hospital study, admission into care was associated with the number of problems faced by supporters and a persisting, high level of strain which was not alleviated by professional support (Gilleard, 1984). We are presently following-up surviving subjects and families to determine whether similar influences play a part in this community group.

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Sex Differences in the Age of Onset of Bipolar Affective Illness

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Data from a UK national sample showed differences between the sexes in age-specific inception rates for mania. Women had a higher inception rate than men during the middle years. The cumulative admission rates were nearly equal between the sexes.

The age of onset of bipolar affective illness has been determined by several investigators. These may be divided into two groups, on the basis of the results obtained. The first group found that the distribution of the age of onset of bipolar affective illness peaks in early adult life (late teens and 20s) and thereafter declines with age (Winokur *et al*, 1969; Angst *et al* 1973; Carlson *et al*, 1974; Loranger & Levine, 1978; Petterson, 1977; Joyce, 1984). The second group (Spicer *et al*, 1973; Eagles & Whalley, 1985), using national figures for first admissions, came to the conclusion that the inception rate for mania increases with age and peaks in late life.

The discrepancy could arise for two reasons. Firstly, the methodologies were different. The former studies were on relatively well defined patient populations, whereas the latter were based on the numbers of patients admitted to hospitals in England and Scotland with a diagnosis of mania. The advantage gained in basing a distribution of age of onset upon a large number of patients is mitigated by the uncertainty regarding diagnostic accuracy and consistency, which is inherent in data pooled from various hospitals and units.

The second reason has to do with fundamental considerations regarding the concept of age of onset of a condition with variable onset such as bipolar affective illness. The former studies were based upon the observed age of onset of bipolar illness. This is obtained by simply noting the age of onset of a consecutive series of patients. The sample so obtained will contain an excess of individuals with early onset, if only because early-onset individuals would be expected, on average, to live longer after onset than those whose illness begins in old age. Thus, if we learn that a sample of patients with bipolar illness (or any other illness) has an individual whose illness started, say, over 50 years previously, we can conclude that the person concerned had onset in early life. On the other hand, someone whose illness started a year previously is just as likely to have had onset at age 20 as at 70. The time between onset and index admission for early-onset bipolar patients would therefore be expected to vary much more than that in the late-onset group. The data of Winokur *et al* (1969) lends support to this hypothesis. Twenty of their 61 patients with bipolar illness had onset before age 20. The differences between the ages at onset and at index episode for each of the 20 patients ranged from 0 to 33, with a mean of 9.7 years. The corresponding figures for the six patients with onset after age 50 were a range of 0 to 14 and a mean of 3.8 years.

It is therefore necessary to restrict the sample to patients whose illness started at the same time, thereby ensuring that all have an equal chance of being included in the sample, irrespective of age of onset. Another reason that any sample of bipolar patients might contain an excess of early-onset cases is that younger people outnumber older people in the general population. In order to obtain a meaningful estimate of the probability of developing symptoms at a given age, it is necessary to determine the age-specific inception rate, as Eagles & Whalley (1985) and Spicer *et al* (1973) have done.

Previous studies on the sex differences in bipolar affective illness have yielded an excess of women relative to men (sex ratio approximately 1.3 : 1) and a lower mean age of onset in women compared with men, although the differences do not reach statistical significance (Perris, 1968; Gershon *et al*, 1975; Paterson, 1977; Loranger & Levine, 1978; Angst *et al*, 1980; Joyce, 1984). Baron & Risch (1983) found a later mean age of onset in women. These findings are intriguing, as they are mostly based on the observed age at onset. The population age distribution of women is different from that of men, with a preponderance of elderly women over men. If there were no differences between the sexes in the age-specific inception rate of bipolar illness, one would expect differences in the observed age at onset, and vice versa. There is a possibility that differences between the sexes in age of onset of bipolar illness have not been highlighted because studies have been based on the observed age at onset.

The object of this study was to determine whether there are any differences between the sexes in the age of onset of bipolar affective illness, using data from a national sample.

Method

Psychiatric hospitals and units in England are required to submit information, including diagnosis, age, and sex, about in-patients to the Department of Health. The information is collated and stored at Norcross, Blackpool, under the heading "The Mental Health Enquiry" and forms the basis for the annual *Inpatient Statistics from the Mental Health Enquiry*, published by Her Majesty's Stationery Office. The diagnoses are coded according to the latest edition of the World Health Organization's *International Classification of Diseases*. Since 1980 ICD-9 has been used (World Health Organization, 1978). Unpublished data from the Mental Health Enquiry were made available to the author by the Department of Health and these form the basis of this article. This is the same type of data as used by Eagles & Whalley (1985) and Spicer *et al* (1973).

Results

The number of first admissions, by age and sex, for ICD-9 category 296.0 manic-depressive psychosis, manic type, for the years 1982-86 inclusive, was noted. The age-specific inception rate (new admissions per million of the population for each five-year age interval) was computed (Table I).

TABLE I

First admissions for manic-depressive psychosis[1] by age and sex, 1982-86 (means of annual statistics)

Age interval: years	*No. of first admissions per year*		*Population of England and Wales (×1000)*		*Inception rate per million per year*	
	female	*male*	*female*	*male*	*female*	*male*
10–14	0	0.6	1711.8	1808.5	0	0.3
15–19	24.6	25.6	1967.8	2074.4	12.5	12.4
20–24	56.2	55.8	1994.2	2043.8	28.8	27.3
25–29	53.2	49.4	1744.4	1776.8	30.4	27.8
30–34	47.4	37.4	1683.4	1705.4	28.2	22.0
35–39	47.2	36.4	1800.6	1812.0	26.2	20.1
40–44	44.8	28.6	1470.8	1495.0	30.5	19.1
45–49	43.0	28.0	1375.8	1391.4	31.2	20.1
50–54	34.2	25.2	1360.4	1355.2	24.2	18.6
55–59	33.6	28.0	1403.8	1352.0	24.0	20.7
60–64	33.4	22.8	1471.4	1326.0	24.4	20.2
65–69	30.2	22.8	1253.6	1039.4	24.2	21.9
70–74	31.4	20.0	1227.8	903.4	25.6	22.2
75–79	27.6	15.6	997.8	605.0	27.6	25.8
80–84	14.0	8.8	657.6	302.2	21.2	29.3
85+	11.2	3.8	456.6	138.6	24.4	27.7
Total	532.0	408.8	–	–	383.4	335.5

1. ICD-9 code 296.0.

A two-way analysis of variance was performed. There were differences between the sexes in age-specific inception rate ($F=6.54$, $P<0.05$) but no significant year-on-year differences. The female : male ratio in age-specific inception rate was noted, and the following observations made.

(a) The ratio of cumulative inception rates was (women : men) 1.14. The ratio in numbers of admissions (i.e. before adjustment for the population age structure) was 1.30. This suggests that failure to take population age differences into account results in an overestimate of the overall female : male ratio.

(b) In early life, the inception rate for men and women is nearly equal. The female preponderance reaches a peak in middle life and thereafter declines (Fig. 1). The female : male ratio varies from 1.59 to 0.88; however, none of the points on the curve lies outside the 5% confidence intervals from the regression line.

Discussion

Information from the Mental Health Enquiry has a number of drawbacks. It is not comprehensive; approximately 15% of psychiatric hospitals and units fail to submit information. In many cases the ICD codes are assigned by clerical staff at the Department of Health, Norcross, Blackpool, on the basis of the information on the forms, rather than by the clinicians treating the patients (personal observation). There is often insufficient information to permit exhaustive categorisation. The largest categories often comprise miscellaneous cases that are difficult to classify, for example 311.9, depressive disorder not elsewhere classified. The resulting loss of information will vary according to the illness under study. It would be expected to be smaller in the case of mania than in depression (there is no category 'mania not elsewhere classified' outside the category of affective

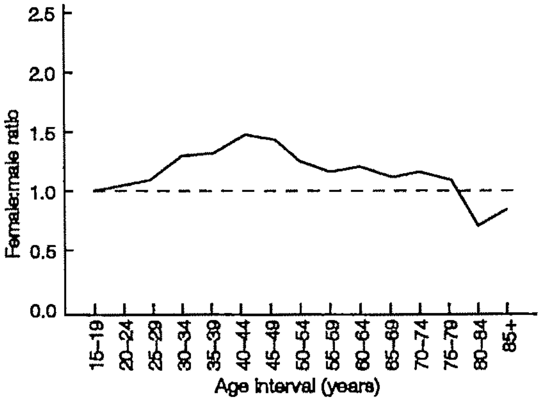

FIG. 1 Female : male ratios of age-specific inception rates.

psychosis). The category manic–depressive psychosis other and unspecified (296.6–296.9) probably includes some cases of mania as well as depressive and mixed affective states. The frequency of these categories in the Mental Health Enquiry is about half that of 296.0, manic–depressive psychosis, manic type. In contrast, the frequency of 311.9, depressive disorder not elsewhere classified, is half as much again as 296.1, manic–depressive psychosis, depressed type, and 300.4, depressive neurosis, together. The distribution of ages at first admission would be affected by misclassification if the latter is an age-dependent phenomenon, that is if patients of a certain age at first admission are more likely to receive a diagnosis other than mania or to be coded under 'other and unspecified'. Joyce (1984) found that patients with early-onset bipolar affective illness were more likely to receive a diagnosis of schizophrenia than those with later onset.

The study of Spicer *et al* (1973) yielded results that support the conclusions of the present study regarding the age variation in sex differences in inception rate for mania. Eagles & Whalley (1985) did not find sex differences in age at onset, but their sample was smaller.

The aetiology of bipolar affective illness is probably multifactorial, with contributions from genetic, biological, and psychosocial factors. Examination of the distribution of age of onset leads to speculation about some of the factors that precipitate symptoms. Absence of illness before puberty has been noted by several writers (Anthony & Scott, 1960; Crowe & Smouse, 1977; Loranger & Levine, 1978; Joyce 1984) and suggests a role for hormonal factors. It is interesting to note that the cumulative inception rate is nearly equal for men and women. This suggests that the liability to bipolar illness is similar between the sexes, and the observed excess of women with illness is attributable to life experiences and demographic factors. This is consistent with the conclusion that the preponderance of women with affective illness cannot be accounted for by an increased genetic loading (Merikangas *et al*, 1985).

Stressful life events have been noted to be associated with the onset of manic episodes (Ambelas, 1979). Johnson & Leeman (1977) found pregnancy and the puerperium to be the commonest stress factors associated with an initial episode in bipolar patients. It is therefore scarcely surprising that women have a higher inception rate during the middle years (Fig. 1), a period which includes the reproductive years. The menopausal years coincide with late middle life, a time associated with an excess inception rate among women. Organic cerebral abnormalities have been associated with manic episodes in late life (Shulman & Post, 1980). These factors are of importance in both men and women; this is consistent with the observation that the female preponderance in inception rate decreases in late life.

The classification of the affective psychosis into unipolar and bipolar forms has wide acceptance in psychiatry, and is underpinned by numerous observations (Andreasen, 1982). There are some similarities between the two conditions, however, which suggest that they are closely allied. The similarity in inception rate (both show an increase with age, although unipolar illness has a steeper slope) has been pointed out by Eagles & Whalley (1985). There is, in addition, a similarity in the pattern of sex differences in inception rate. The data of Eagles & Whalley (1985) and Spicer *et al* (1973) suggest that the excess of females over males in inception rate for depressive illness is minimal in early life, increases with age, and declines in late life. This is similar to the pattern seen in mania, with the exception that the female peak occurs at an earlier age in mania than in depression.

Most of the studies reviewed in this article have been based on admissions statistics. They can serve only as a guide to inception rates since they have some inherent deficiencies – for example, previous episodes of illness not leading to hospital admission are neglected. In a study of hospital case notes, the author identified 149 patients (84 women, 65 men) meeting DSM–III criteria for bipolar illness (unpublished data). Twenty-three of the women had had episodes of illness, before the first admission, mostly depressive in nature and associated with pregnancy. Ten of the men had had an episode of illness before first admission. This suggests that inception rates based on admissions underestimates the female preponderance, at least during the early (reproductive) years.

The results of this study, in view of the caveats mentioned above, must not be regarded as definitive, but merely as indicative of unanswered questions and issues to be clarified. A large, prospective study, on a well defined patient population, may shed light on sex differences in age of onset (rather than just age of first admission) of bipolar illness, and the factors underlying such differences.

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An Increase in Violence on an Acute Psychiatric Ward
A Study of Associated Factors

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The increase in violent incidents on an acute psychiatric ward over a 15-month period was found to be strongly associated with the increase in use of temporary nursing staff ($r = 0.63$; $P = 0.0005$). The change in staffing patterns accounted for 39% of the variance in violence. An examination of the characteristics of all patients admitted to the ward revealed that the violent patients were significantly younger, more likely to have been admitted compulsorily and less likely to be depressed than non-violent ones.

Violence is a serious problem for those working in the Health Service (Department of Health and Social Security (DHSS), 1988). It is commonly encountered in caring for the mentally ill, particularly in hospitals (Solloff, 1983; Tardiff, 1984; Haller & Deluty, 1988). It has considerable implications for the organisation of services, as well as for the individuals involved. Earlier British reports suggest that the level of 'serious' violence is low, and that only a small proportion of patients are involved in violence of any kind (Fottrell *et al*, 1978; Fottrell, 1980; Armond, 1982; Pearson *et al*, 1986). Yet, there is a growing body of concern, particularly in the USA, that levels of violence may be increasing (Edwards & Reid, 1983; Tardiff, 1983; Adler *et al*, 1983; Haller & Deluty, 1988; DHSS, 1988). It is surprising in the circumstances that the literature on violence in psychiatric wards is sparse (Fottrell, 1980; Ionno, 1983; Edwards & Reid, 1983).

Important differences in methodology and design between studies render comparison of their findings difficult (Ionno, 1983; Haller & Deluty, 1988). There is no generally accepted definition of violence. Some reports include verbal abuse or threatening behaviour (Bouras *et al*, 1982*a*; Werner *et al*, 1983), others damage to property (Armond, 1982) and self-harm (Fottrell *et al*, 1978). Some investigators are concerned with physical attacks on persons (Schader *et al*, 1977; Dietz & Rada, 1982, 1983; Tardiff, 1984) while others limit their interest to attacks on staff (Ruben *et al*, 1980; Aiken, 1984; Hodgkinson *et al*, 1985). Each study examines a different population. Characteristics vary with size of hospital, specialisation of facility, patient group and area served. There are also important differences in the methods used for collecting data. A further problem with many studies is that violent patients have been examined without reference to the non-violent group (e.g. Fottrell, 1980; Ruben *et al*, 1980; Armond, 1982). It would not be surprising, for instance, to find more schizophrenics among the violent in a hospital where most patients are schizophrenics (Haller & Deluty, 1988).

Despite these difficulties, some tentative conclusions may be drawn. Violence is more likely to be associated with younger patients (Tardiff & Sweillam, 1979; Depp, 1983; Hodgkinson *et al*, 1985), schizophrenics (Schader *et al*, 1977; Tardiff & Sweillam, 1982; Hodgkinson *et al*, 1985; Pearson *et al*, 1986), and those with a history of violence before admission (Conn & Lion, 1983, Yesavage, 1983, 1984; McNiel *et al*, 1988). No consistent associations have been found with sex or race. It has been suggested that increased violence may be associated with increased rates of admission (Adler *et al*, 1983) and overcrowding (Dietz & Rada, 1982; Edwards & Reid, 1983). This has not been demonstrated quantitatively, and one study reports an increase in violence as the ward population declined (Kalogerakis, 1971). No consistent association has been shown between length of stay and violence (Dietz & Rada, 1982).

Adequate provision of well trained staff is thought to be important in the prevention of violence (Brailsford & Stevenson, 1973; Depp, 1983), but there is no quantitative evidence to support this hypothesis. Hospitals suffering 'disasters' tend to have a poorer staff:patient ratio than most others (Yates, 1981; Martin, 1984), but no direct association is evident. In fact, those few studies documenting staffing levels have shown an increase in violence when the ward population declined, so that the staff:patient ratio increased (Melbin, 1969; Kalogerakis, 1971; Depp, 1983).

Factors that may diminish the ability of nursing staff to manage disturbed patients include: authoritarian attitudes and underinvolvement of medical staff (Brailsford & Stevenson, 1973; Langley & Bayatti, 1984); increased vulnerability among nurses involved in staff conflict (Adler *et al*, 1983; Morgan & Priest, 1984); poor communication among staff

(Brailsford & Stevenson, 1973; Packam, 1978); and demoralisation and incompetence among staff with a high turnover rate (Depp, 1983).

In one study, more violence was shown when a ward was operated as a therapeutic community than when run along traditional lines (Bouras *et al*, 1982*a*), although the preferability of the therapeutic community with regard to violence has been advanced (Levy & Hartocollis, 1976). No significant association was found between medical and nursing staff changes and patient dissatisfaction or uncooperative behaviour (Bouras *et al*, 1982*b*). Nurses with least experience were attacked most often in one study (Hodgkinson *et al*, 1985) and least often in another (Fisher, 1988). It has been claimed that training staff in aggression-control techniques can significantly reduce the incidence of injury (Infantino & Musingo, 1985). Yet, in a different study, nurses who had attended violence training seminars reported being assaulted twice as often as those who had not (Fisher, 1988).

An apparent increase in the number of violent incidents on the acute admission ward of our psychiatric unit prompted a quantitative evaluation of the problem. The aims of the study were: to ascertain the level of violence on the ward and the nature of any increase; to compare the characteristics of those patients involved in violence with those not involved; to examine factors concerning the patients or their care which may have been associated with an increase in violence; and to identify possible avenues for future intervention towards the reduction of violence.

Method

Location

The study was performed in a 60-bed psychiatric unit attached to a district general hospital in Paddington, London. The unit is responsible for a catchment area population of 70 700 according to the 1981 census. The district is one of high social and psychiatric morbidity and ranks as either the second or fourth most deprived of the 192 districts in the country, depending on the indices used (Department of Environment, 1983; Jarman, 1983). The unit caters for acute general psychiatric problems and does not contain any long-stay wards.

A 12-bed 'high-dependency' ward was selected for study; this has a higher nurse:patient ratio than the other wards in the unit and a door that can be locked. It caters for new admissions and provides a facility for patients requiring close supervision. Patients are transferred to other wards as soon as their mental states and behaviour permit. The potential for violent behaviour is thus concentrated on the 'high-dependency' ward, and incidents involving violence are far fewer in other parts of the unit.

Definition and documentation of violence

Violence was defined as any act of actual physical aggression involving physical contact, irrespective of outcome. Incidents of violence were categorised into four groups according to the target of the assault: those directed against fellow patients, staff, the self, and property.

All incidents of violence occurring on the ward during January 1986–March 1987 inclusive were examined using a retrospective design. The number and nature of violent incidents were ascertained from the standard ward incident forms which are completed by nursing staff and countersigned by a doctor whenever any untoward incident occurs. In order to detect any variation in the threshold for reporting incidents, two further measures were adopted. Firstly, details were collected in the same manner of all incidents recorded which did *not* involve violence in order to determine whether or not these varied over time in parallel with violent incidents. These non-violent incidents concerned minor accidents and such events as grand-mal fits. Secondly, using the incident forms and ward ledgers, the nature of the violent incidents was examined in order to see whether the type of incidents recorded had changed.

Comparison of violent and non-violent patients

In the first part of the study, the 15-month period was examined as a whole and detailed information was gathered about violent and non-violent patients (sex, age, race, legal status on admission and diagnosis (diagnoses were recorded initially as ICD-9 (World Health Organization, 1978) categories which were then amalgamated to form broader groups)). The characteristics of the violent and non-violent groups were then compared using the χ^2 test (two-tailed), corrected for continuity.

Examination of the increase in violent incidents

In the second part of the study, the 15-month period was examined month by month. As well as the number and type of violent and non-violent incidents, the following data were recorded: the average number of beds occupied on the ward each month; the number of admissions to the ward each month; details of all violent and non-violent patients admitted to the ward each month (age, sex, race, legal status on admission, and diagnosis); identical details of all violent and non-violent patients occupying a bed on the ward in any given month; the average weekly nursing provision including 'units' of permanent nursing staff (one unit = 37½ hours), units of agency (temporary) nursing staff, and total number of shifts worked by agency staff (since examination of the times of incidents confirmed reports that very few occur at night (Fottrell, 1980; Dietz & Rada, 1983; Pearson *et al*, 1986; Shah & Piachaud, 1988), only daytime shifts were investigated); the timing of the rotation and leave of junior doctors and the timing of consultants' absences.

The results of these inquiries were tabulated and analysed using a conventional non-parametric statistical test of association (Kendall's rank correlation coefficient).

TABLE I

A comparison of the characteristics of violent and non-violent patients

	Violent patients (n=64)		*Non-violent patients (n=216)*		χ^2
	n	%	n	%	
Sex					
male	31	48.4	111	51.4	NS
female	33	51.6	105	48.6	
Age: years					
<25	25	39	46	21.3	9.86 (2 d.f., $P=0.0072$)
25–49	27	42.2	135	62.5	
>50	12	18.75	35	16.2	
Race					
Caucasian	42	65.6	158	73.1	NS
Afro-Caribbean	19	29.7	46	21.3	
Asian	1	1.5	10	4.6	
Far-Eastern (Asiatic)	2	3.2	2	1.0	
Principal diagnosis: ICD-9					
schizophrenia	39	60.9	112	51.85	NS
mania	11	17.2	18	8.3	NS
depression	1	1.5	23	10.65	4.11 (1 d.f., $P=0.0427$)
personality disorder	6	9.0	25	11.6	NS
alcohol/drug abuse	5	7.8	22	10.2	NS
organic disorder	2	3.2	10	4.6	NS
other	0	0	6	2.8	NS
Legal status on admission					
compulsory	39	60.9	94	43.5	5.33 (1 d.f., $P=0.021$)
informal	25	29.1	122	56.5	

Results

Number and type of violent incidents

Over the 15-month study period, 102 violent incidents were recorded, together with 25 non-violent incidents. Violence against staff ($n=44$) and against other patients ($n=24$) ranged from fist fights to one case of rape. Incidents of self-harm comprised poisoning ($n=4$), cutting ($n=6$) and attempts at hanging ($n=4$). Those against property ($n=20$) consisted of the destruction of furniture, fabric and fittings and the setting of fires ($n=5/20$).

Comparison of violent and non-violent patients

Of the 280 different patients admitted to the ward during the study period, 64 (23%) were responsible for incidents of violence. The characteristics of the violent and non-violent groups are presented in Table I.

Most of the violent patients were Caucasian (65.6%) and schizophrenic (60.9%). The sex distribution was approximately equal, 81.2% were aged below 50, and 60.9% had been admitted compulsorily under the Mental Health Act (1983). Comparisons between violent and non-violent groups using the χ^2 test showed a number of significant differences. The violent population were more likely to be under the age of 25 ($\chi^2=7.32$; 1 d.f.; $P=0.0068$), to have been admitted involuntarily ($\chi^2=5.33$; 1 d.f.; $P=0.021$) and not to be depressed ($\chi^2=4.11$; 1 d.f.; $P=0.0427$). No significant differences were detected with regard to sex, race or diagnostic category. In particular, schizophrenics were not significantly over-represented in the violent group when the composition of the non-violent group was taken into account.

Examination of the increase in violent incidents

Over the 15 months, there was a substantial increase in the number of violent incidents, but no concomitant increase in the number of non-violent incidents. The number of violent incidents in the second half of the period constituted a 240% increase over the number in the first half ($\chi^2=15.53$; 1 d.f.; $P<0.0001$). No change was detected in the severity of violence reported or in reporting levels. The increase in incidents was approximately equally distributed between all four categories of violent behaviour.

The proportion of the ward population involved in violent incidents increased in parallel with the number of incidents (Fig. 1).

The proportion of permanent nursing staff halved over the study period. In order to maintain a constant staffing level, an increasing number of temporary (agency) nursing staff were employed. During the 15 months, the agency provision more than trebled in terms of nursing units and

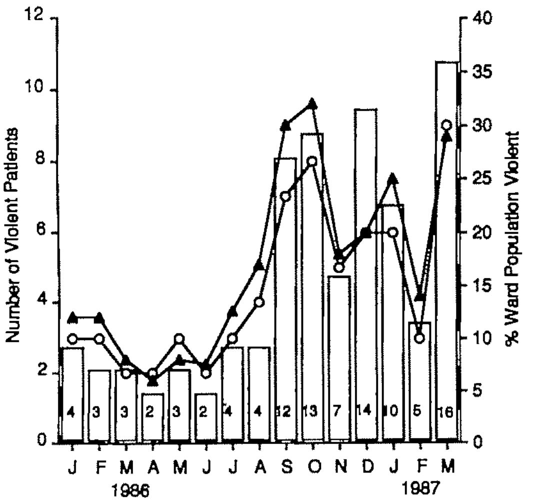

FIG. 1 Graph showing number of violent incidents ▨ , number of violent patients (— ▲ —) and proportion of ward population involved in violent incidents (—○—) each month.

number of shifts worked, such that the agency provision came to exceed the permanent provision ten months into the study period (Fig. 2). There was a positive correlation between number of violent incidents and agency nursing units ($r=0.57$; $P=0.0018$) and agency nursing shifts ($r=0.63$; $P=0.0005$) and a negative correlation between number of violent incidents and levels of permanent nursing staff ($r=-0.62$; $P=0.0007$).

There were no significant correlations between the number of violent incidents and admission rates or bed occupancy, either in global figures, or stratified by age, sex, race, diagnostic category and legal status on admission.

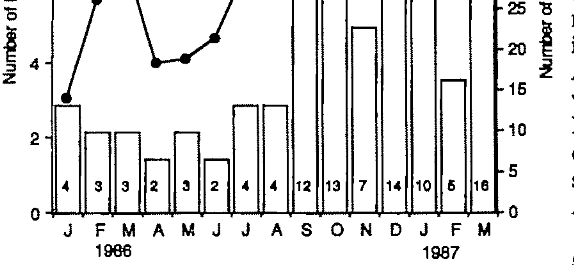

FIG. 2 Graph showing number of violent incidents ▨ , and changes in nursing provision (— ● —) Number of agency shifts (weekly average), (— △ —) number of nursing units (weekly average, permanent nurses only) (1 unit = 37½ hours)).

Junior medical staff changeovers occurred in February and August. Peak leave months were January and June. There was no evident relation between these times and increases in violence. Consultant absences were evenly scattered through the period.

Discussion

A greater than threefold increase in violent incidents occurred on the 'high-dependency' ward over the study period. This was strongly associated with a decline in permanent nursing staff and an increase in the number of agency staff, despite the maintenance of a constant nursing complement. There were only small correlations between levels of violence and other factors including changes in admission rates and bed occupancy, analysed according to a variety of demographic and diagnostic variables, and taking account of medical staff changes and seasonal factors. The results suggest that 39% of the variance in violent incidents (r^2) was associated with changes in staffing patterns. We can find no similar study with which to compare our findings.

There were 102 incidents in all, of which 65 took place in the final six months of the study. Sixty-eight involved attacks on people, staff being attacked twice as often as patients. This level of violence is high in comparison with previous reports (Fottrell, 1980; Pearson *et al*, 1986). However, it is broadly similar to that found in an inner-city locked ward by Aiken (1984). Many other authors have found that only a small proportion of patients are involved in violence. This was not the case on our ward, where 23% of those admitted during the study period engaged in acts of violence.

Incident forms were used to ascertain the number of incidents of violence. Lion *et al* (1981) suggested that there is a significant under-recording of violence on incident forms. Aiken (1984) failed to confirm Lion *et al*'s findings, reporting a discrepancy of only 5% between the number of incidents recorded on his research questionnaire and the number recorded in routine ward documentation. It is of note that Aiken's observations were made on a 17-bed ward with a relatively small team of nursing staff, whereas Lion *et al*'s finding related to a state mental hospital of diverse wards with 1500 beds and 800 nursing staff. Our 12-bed ward is comparable with that of Aiken's study.

It is possible that the increase in temporary nursing staff might have led to higher rates of reporting incidents owing to a preponderance of less experienced nurses with a lower threshold for reporting incidents. However, an examination of the quality of the incidents over the 15 months failed to reveal any such change and there was no concomitant increase in the reporting of non-violent incidents which would have been expected if reporting thresholds had been progressively lowered.

Comparison of the characteristics of the violent and non-violent patients suggests that younger patients (aged 25 years or less) are more likely to be violent than older patients. The younger of the violent patients were more often responsible for more than one violent incident. Although this confirms the findings of other studies, the reason for this age difference is not clear. Tardiff & Sweillam (1979) suggest that differences in the incidence of disorders between age groups may be an important factor, with schizophrenia, personality disorder, transient situational reactions and secondary problems of drug abuse being more common in the young. However, no such differences in our study reached significance although numbers were relatively small. Furthermore, violent crime is more common among young people generally.

Unlike some previous reports, no single diagnostic category was found to be positively associated with violence. The majority of the patients were schizophrenics and the sample sizes in the other diagnostic groups may have been too small to detect real differences. Interestingly, all the incidents of self-harm ($n=14$) were perpetrated by schizophrenics ($\chi^2=9.48$; $P<0.005$), which supports evidence suggesting a high suicidal potential for this group. Patients with a diagnosis of depression, with or without active psychotic phenomena, were significantly less likely to be violent ($\chi^2=4.11$; 1 d.f.; $P=0.0427$). Yesavage *et al* (1981) have suggested that violence is associated with 'disordered thinking'. If one tentatively accepts the hypothesis that psychosis is important in violence, we would suggest that this category does not include those patients suffering from depressive illness.

Patients admitted involuntarily under the Mental Health Act 1983 proved significantly more likely to engage in violent acts. This probably reflects the fact that the danger of harm to the self or others is one of the principal criteria used by psychiatrists in deciding whether the powers of the Act should be invoked.

The significance of correlations concerning variables which change over time is difficult to interpret using conventional techniques, as these do not allow for the possible effect of time itself (Gibbons & Davis, 1984). Yet, time factors neither influence the degree of correlation, nor affect the absence of significance with conventional tests. The strong association between nursing levels and violence is highly suggestive of a link between the two although the nature of this is open to interpretation. It is possible that the rise in violence might have led to the changes in staffing, as permanent staff decided to seek employment elsewhere. Yet, the nurses who left our unit indicated that this was not the case.

Various suggestions may be advanced as to why the decline in permanent staffing might lead to an increase in disturbance among patients. Disturbed patients are in need of stability and continuity around them (Armond, 1982; Crammer, 1984). Drinkwater (1982) speculated that if staff interact less with more severely disturbed patients, then extreme behaviour such as violence may be the most effective way for them to gain attention. Factors said to be important in the prevention and management of violence include a consistent approach, with defined roles for each member of staff (Aiken, 1984), the presence of staff capable of setting reasonable limits for behaviour (Adler *et al*, 1983), and training in techniques of aggression control (Infantino & Musingo, 1985). Temporary nurses with a variable amount of training, no previous knowledge of the patients and little familiarity with the ward or its procedures tend to be uncertain and uncoordinated in their dealings with patients and staff alike. In these circumstances, nurses may adopt a more custodial and less therapeutic role with the patients, as evidenced in this study where the door of the ward, which was almost always open until mid-1986, was thereafter almost permanently closed. This in turn may have added to the frustration among patients (Folkard, 1960). There is some evidence in the literature to suggest that patients behave aggressively when they are bored and not involved in therapeutic activities (Ekblom, 1970; Fottrell, 1980; Pearson *et al*, 1986). On our ward, there was a noticeable decline in provision of activities for the patients owing largely to the absence of sufficient permanent nursing staff to encourage and organise such events. At the end of the study, not even the television remained, having been destroyed by a patient.

Other possible reasons for the increase in violence were explored in detail. It was not simply the result of the admission of a few particularly violent individuals, since the number of patients involved increased in parallel with the number of incidents (Fig. 1). There was no change in catchment area or medical provision. Changes in the ward population in terms of diagnosis, age, sex, race and involuntary admission showed no trend over the study period. Ward usage in terms of bed occupancy and rate of admission likewise showed no trend. It has been suggested that changes in the prescription of medication may be reflected in levels of violence (Yesavage, 1982). Changes in junior doctors on our unit might have involved changes in prescriptions. However, there was no relationship between staff changeovers and levels of violence. The unit studied serves a population with an unusually high level of socioeconomic difficulties and 'problem behaviour' (National Health Service Health Advisory Service, 1988). However, this was so throughout the study period. Physical assaults have increased in England and Wales by 7% each year for the last ten years (Her Majesty's Stationery Office, 1985), but it is highly unlikely that such trends in the general population could explain the 240% increase in violence on our ward between the two halves of the study period.

Conclusion

Changes in behaviour within institutions are rarely due to one factor alone (Watson & Bouras, 1988). It is likely that the increase in violence on the ward was the result of a complex interaction of factors, including nursing provision. Yet, the association between the decrease in permanent nursing numbers and the increase in violence is of particular interest. Whereas many of the characteristics of in-patient populations and the other variables discussed above are not amenable to change through planning, staffing consistency offers a possible intervention in the prevention of violence on psychiatric wards.

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The Patients' View of Life in a Psychiatric Hospital

A Questionnaire Study and Associated Methodological Considerations

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In any assessment of hospital life, the patients' view is indispensable, but there is no generally accepted way of seeking it. In this study, the views of 258 patients in four 'traditional' English psychiatric hospitals were obtained by a questionnaire of 45 items supplemented by freehand comments. Their experience of fellow patients, the staff and the material and institutional aspects of hospital care were explored. Some of the benefits and problems of questionnaire use in this realm are discussed.

Admission to psychiatric hospital is a momentous event for any patient. Despite the less restrictive Mental Health Act of 1983, a significant proportion are still admitted compulsorily, and in the National Health Service, informal patients have no choice of hospital. We wished to learn more about patients' experience of hospital life, partly to understand it better and partly in the hope of improving it.

Studies of the quality of psychiatric hospital care published before 1980 have been fully reviewed by Weinstein (1979, 1981). Over the years, the psychiatric hospital has been seen in a changing light: in the 1950s it was viewed as an institutional community, in the 1960s as a therapeutic community, and more recently as part of a consumer service. Methods of investigation have also changed. Initially, it was thought that the patients were so crushed by the institution that they were incapable of criticising it. This was done on their behalf by sociologists masquerading as patients or obtaining employment in the hospital; they delivered a resounding condemnation (Goffman, 1961; Rosenhan, 1973). Later on, in keeping with the spirit of the therapeutic community, patients were encouraged to speak for themselves, and some of their more expressive comments have been published (Kotin & Schur, 1969; Raphael & Peers, 1977). Moos (1969) and Moos & Houts (1968) treated the hospital ward explicitly as a therapeutic community, but favoured the questionnaire – the patient still speaking but now on the investigator's terms. Most recently, particularly in the USA, the psychiatric hospital has been viewed as an item of consumer service (Kotin & Schur, 1969; Eisen & Grob, 1979).

Most of the studies of the patient's view of psychiatric hospitals have been conducted in the USA and were published in the 1950s and 1960s (Soulelem, 1955; Reznikoff *et al*, 1959; Rice *et al*, 1963; Keith-Spiegel *et al*, 1970). There have also been two British publications in recent years (Raphael & Peers, 1977; Gordon *et al*, 1979). Gordon *et al* (1979) suggest that this dearth is due to the fact that the British system of health care "militates against the consumer voice".

Method

The investigation consisted of four parts: a questionnaire consisting of 54 statements (of which nine were not analysed); an invitation to make additional freehand comments on a sheet of A4 paper; a question on ward/sex preference; and a question on delay in receiving money. As a preliminary to writing the questionnaire, patients and staff were asked to advise on aspects of hospital life which might cause distress or affect well-being. Statements based on this advice were composed to replicate as far as possible what a patient might say, if moved to comment (Oppenheim, 1966). The traditional Likert (1932) five-point response scale (strongly agree – strongly disagree) was used. The statements were written in order to identify experiences rather than to convey opinions. Thus, for instance, "I sometimes have to wait far too long for a ward toilet to become free" (statement 45, see Appendix) was preferred to "There are not enough toilets on the ward". It was suspected that the "not enough" formulation might bias answers, because of a tendency to be in favour of what is indisputably good. We therefore tried to avoid this form of statement as far as possible. Although grammatically negative statements are often used to make complaints, with one mild exception (statement 35, see Appendix), we eschewed them: they are more difficult to understand than affirmatives (Wason, 1959; Slobin, 1966; Sherman, 1973), probably because of an unusual feature of negative usage in the English language (Akiyama *et al*, 1979), and they can lead to response errors (Griffiths *et al*, unpublished).

Half the statements were constructed to express sentiments unfavourable to the hospital, half favourable (the Appendix statements do not show this ratio exactly because some unsatisfactory items were dropped). The methodological nicety of placing items in random order was rejected in favour of a topic-by-topic development, starting with the physical aspects of the ward as a relatively gentle introduction. (The Appendix does not list the statements in this order.)

The patients

The patients studied were a separate group from those whose opinions had been originally sought. The major part of the investigation was conducted in the hospital in which the authors worked (Hospital 1). This is a traditional psychiatric hospital of 375 beds, opened in 1843, serving a mixed rural and urban population of 400 000. To avoid being too parochial, the investigation was extended to three other similar hospitals, two serving mixed rural and urban populations (Hospitals 2 and 3), and one an urban population (Hospital 4). These hospitals had opening dates between 1870 and 1919 and contained between 200 and 380 beds. An undertaking was given to the relevant ethics committees not to approach patients deemed by the staff to be too disturbed for the questionnaire and subsequent probing. The authors did not make this decision themselves. These patients apart, all consenting patients who were near discharge after a stay of more than five days on the acute wards of the four hospitals were studied for continuous, but varying, periods. In the case of one hospital, the continuous period amounted to two visits only.

Procedure

After the patients had completed the questionnaire, individual statements were probed to determine whether they had been understood in the way intended. Since we were not confident that we could identify which statements might be misunderstood, we used pre-selected (Schuman, 1966) rather than discretionary probes. Before each interview, 16 statements were selected at random (with the restriction that over the course of all the interviews each statement was selected equally often). To obtain an estimate of the response error, the 16 selected statements were presented with slightly altered wording. Spearman rank correlation coefficients were then calculated between the scores of patients on these items and their scores on the original items. These 16 statements, and those which had not been answered, or which bore a first answer crossed out, were then probed. When a statement had not been answered through oversight, the answer derived on probing was used for the analyses. The patients were guaranteed anonymity, and were given the opportunity either to decline to partake ($n = 13$) or to abandon the questionnaire after the first 20 items ($n = 12$).

Analyses

Responses to the statements were scored 1–5 (1 = response least favourable to the hospital). The data were analysed with a Minitab program (Ryan *et al*, 1985) version 5.1.1. for MS-DOS micros.

Nine of the 54 statements were not analysed because they were judged unsatisfactory or defective. Two of these were on the benefits and adverse effects of drug treatment. On such technical topics which require clinical trials for valid inferences, the patient does not have an adequate "basis for testimony" (Payne, 1980). The others were excluded because they were too vague. To give one instance: an 18-year-old girl had remarked some years earlier "I feel safer in this hospital than I do outside", but 'safer' proved too vague a concept. Summary statistics of the remaining 45 statements are set out in the Appendix. Of them, 42 relate to the hospital itself. In the interests of reducing the rather high variable : patient ratio (Kendall, 1975), these 42 variables were reviewed for exclusion. Only one was dropped (S24) on the grounds, perhaps a little arbitrary, that its topic had been raised, not by the patients in the preliminary enquiry, but many years ago by a senior administrator. Out of interest, however, it is included in the Appendix where it will be seen to have attracted little adverse comment. Principal components were derived from the within-hospital covariance matrix of the remaining 41 items.

Fifteen patients were excluded because they were unable to concentrate. They responded to probing for clarification (Atkinson, 1967) by frequent changes of answer; several admitted to feeling confused. Their exclusion left n values of 161, 34, 29 and 19 for Hospitals 1 to 4 respectively.

The question whether the four hospitals could be regarded as a homogeneous set was examined by profile analysis of the 41 item scores (Morrison, 1978). Hospitals 1 and 2 did not differ significantly from each other either in profile ($F(40, 154\text{ d.f.}) = 0.93$) or level ($t(193\text{ d.f.}) = 0.27$). Hospitals 1 and 2 did, however, differ significantly from Hospitals 3 and 4 in profile. Although this finding may have been an artifact of the non-normality of the scores, it was thought safest to confine the contrasts between response sets (Table IV) to Hospitals 1 and 2 treated as one group. These contrasts were between the categories for which the statements had originally been composed, namely, staff attitudes (S), material standards (M), the effects of other patients (P) and aspects of the hospital as an institution (I). The 'other' (O) category was not included in the comparison.

TABLE I
General characteristics of the sample (n = 258)

All patients				*Patients previously admitted*		
Age in years Mean (s.d.)	*Sex (% female)*	*Length of stay in days Median (IQR)*[1]	*Proportion previously admitted*	*No. of previous admissions Median (IQR)*[1]	*Years elapsed since first admission Median (IQR)*[1]	*Percentage admitted compulsorily*
43.2(14.7)	56.4%	21(14–35)	66%	2(1–4)	8(4–16.8)	19.5%

[1] Interquartile range: 25th–75th percentile values

TABLE II
Social characteristics of the sample ($n=258$)

Civil status		*Usual domicile*		*Those living with family: no. of people in family*		*Social class*[1]	
Married	41%	Alone		2	37%	1 & 2	29%
Divorced	17%	no fixed abode	1.6%	3	25%	3	42%
Widowed	7%	lodgings	4.7%	4	23%	4 & 5	22%
Separated	8%	own home (and other)	14.0%	5	12%	Unclassed[2]	7%
Single	27%	Not alone		>5	3%		
		family or friends	74.0%				
		hostel or group home	2.7%				
		Unknown	3.0%				

1. Census (1981) *User Guide 227*
2. 'Armed Services' (code 135) or 'Insufficient Information' (code 349)

Results

The general and social characteristics of the sample are set out in Tables I and II.

Ward/sex preferences

Respondents were asked whether they would prefer to be nursed on a same-sex or mixed-sex ward (although this precise terminology was not used – see Discussion). A preference was expressed by 198 respondents, 124 (63%) being in favour of a same-sex ward. Table III shows the details.

A maximum likelihood logit analysis (Dyke & Patterson, 1952; Cox, 1970) showed that all three main effects, sex, median age and current ward-type, were significant ($z=3.6$, $P<0.001$; $z=3.0$, $P<0.005$; $z=6.4$, $P<0.001$ respectively). A preference for same-sex ward was associated with being nursed on such a ward, aged 41 or over, and of female sex. This main effects model was tested for goodness of fit and found to be adequate (χ^2 (4 d.f.)$=2.49$, (NS)), that is, there was no evidence of interactions.

Money

Forty-six patients (17.8% of the total) experienced delay in getting their money while in hospital, a matter which caused distress of varying degrees: 30% 'severe', 35% 'some', 19% 'slight', and 16% none.

Questionnaire items

The range of the 'test/retest' rank correlation coefficients of the retained items was 0.64 to 0.97. The 45 retained statements are listed (Appendix) in ascending order of mean score; the lower the score, the less favourable the response. Four of the first seven are connected with being away from home, family and friends.

Those who administered the questionnaire were all currently working in Hospital 1, and were perceived by the patients as being members of staff. We wished to determine whether this influenced responses to the items which dealt with staff attitudes and behaviour. However, some patients were more generous in their assessment than others, an attitude that tended to pervade their judgment on all the items. This source of bias was controlled by using their

TABLE III
Preference expressed by male and female patients ($n=198$), of median age (41) and over or under median age in different ward types for same sex (SS) or mixed sex (MS) ward

Sex	*Female* (+1)[1]				*Male* (−1)[1]			
Age (years)	*≥41* (+1)[1]		*<41* (−1)[1]		*≥41* (+1)[1]		*<41* (−1)[1]	
Current ward type	SS (+1)[1]	MS (−1)[1]	SS (+1)[1]	MS (−1)[1]	SS (+1)[1]	MS (−1)[1]	SS (+1)[1]	MS (−1)[1]
No. preferring SS ward	39	6	37	3	25	1	13	0
No. preferring MS ward	5	8	8	12	6	6	14	15
Percentage preferring MS ward	11	57	18	80	19	86	52	100

1. The sex, age and ward-type variables with values of +1 or −1 as shown were regressor variables in a maximum likelihood logit analysis. The model was $\text{Log}_e\,(\text{ESS}/\text{EMS}) = -0.19+0.69(\text{sex})+0.57(\text{age})+1.47$ (current ward type) where ESS and EMS are the expected numbers preferring SS and MS wards respectively.

responses to neutral items, that is, those that did not entail any criticism of others. The composite variable – staff items minus neutral items – was contrasted between Hospital 1 and the others. This bilinear comparison (Morrison, 1978) was not significant ($\overline{C} = -0.64$; *s.d.* $= 0.98$; $t(239 \text{ d.f.}) = 0.66$; $P = 0.51$).

A simultaneous comparison of the items was made according to the groupings under which they had been originally compiled. For instance, the P and S comparison was the difference between the sum of the mean score on the 'effects of other patients' (P) items ($n = 5$) and that on the 'staff attitude' (S) items ($n = 15$), the latter being divided by three to allow for the larger n value (Morrison, 1978, p. 135). The results are summarised in Table IV.

All comparisons were significant ($P < 0.01$) except that of S and M. The groups therefore received unfavourable comment in the following descending order: effects of other patients (least favourable); institutional aspects; and material standards/staff attitudes.

It was considered that the three factors in Table II, that is, the respondent's age, sex, and the sex of their fellow ward patients, might influence their perception of these fellow patients, as judged by the five patient-related items. However, none of the main effects or interactions was significant. The correlations between scores on the five items and the length of the respondent's stay was also non-significant.

An exploratory analysis of any relationship between derivatives of the questionnaire item scores and the variables (or groupings) of Tables I and II yielded no significant findings. The derivatives for this purpose were the sum of the scores, their first principal component and, notwithstanding distributional problems (see Discussion), the multivariate complex of the 20 items viewed least favourably.

The first principal component accounted for 21.2% of the variance of the 41-item set.

TABLE IV

Comparison of scores on categories of questionnaire items (staff attitudes (S), material standards (M), effects of other patients (P) and aspects of the hospital as an institution (I))[1]*. Only scores of patients from hospitals 1 and 2 included.*

Categories compared	*Value of of comparison*[2]	*99% Bonferroni limits*[3]
P & S	−3.1	0.85
P & I	−1.4	0.76
P & M	−2.8	0.78
S & I	+4.1	1.38
S & M	+0.5	1.27
M & I	+2.6	1.03

1. The other (O) category excluded
2. Value = sum of mean scores on first category items − sum of mean scores on second category items, corrected for different n values of the two categories
3. 99% confidence limits based on t 0.01/12 (194) = 3.395

Spontaneous comments

One hundred and one (39%) patients recorded freehand comments on the space provided. Twenty-two (22%) of these had words of praise for the experience generally and for the staff in particular, but, with one exception, none had them specifically for the material standards or the institutional or community aspects of hospital life. The exception was the remark "Don't pull the old building down, far more friendly than a low-level breeze-block labyrinth". Sixty-six patients (65%) made a total of 230 unfavourable comments, for the most part reaffirming dissatisfactions already covered in the questionnaire, but sometimes expressed a little more pungently. Of the remaining comments, space allows mention of only a few: "meeting so many people a lot iller than myself – it makes me feel worse"; not enough opportunity to see the doctors; trainee nurses not being mature enough to give any real help; "staff too jolly; cheerfulness is appreciated, jollity is not"; having to go to bed and to get up too early; not enough freedom to make drinks; petty rules; not enough places to go to with visitors; not offered vegetarian food; radio and TV on constantly; poor decor; too many or too few non-smoking areas; wards under-staffed; and finally, "the whole set-up leaves one in no doubt that mental health is right at the bottom of the National Health Service money league".

Discussion

A number of questionnaires intended to obtain the patient's view of various aspects of hospital life have been published (Weinstein, 1979). Ideally, they should contain items which are both universal and topical. Since hospitals the world over vary enormously and are in the process of change, such a requirement is extremely exacting, which may explain why none has been generally adopted. Nevertheless, the self-administered questionnaire has a number of attractions. That a question is asked at all declares its topic a legitimate one for comment, and thus helps to weaken taboos on sensitive issues. It enlarges the scope of the inquiry from what patients can put into words, which may be considerably limited by their illness, to what they can understand. It may enable the respondent to be franker than when faced with an interviewer (Edwards, 1957). It does, however, raise a number of technical problems related to question wording, response error and non-normality of scores.

A major difficulty is that a question may appear satisfactory yet be misunderstood in quite unexpected ways (Belson, 1968). We had a salutary example of this in a preliminary phase of the investigation. A minority of patients took "same-sex ward" to refer to the sex of the nurses. Several statements were dropped because their wording was unsuitable, and "medical staff" (S20) would have been better as "doctors". We could discover no major defect with the remainder, although to have all questions understandable to all potential respondents is an unattainable ideal (Kidder, 1981). The following were not understood by a minority: "pros and cons" ($n = 2$), "one of the herd" ($n = 2$), "cooped up" ($n = 1$).

Since the respondent is both the subject and the instrument of observation, measurement errors are inevitable. They will arise through failure to concentrate, distraction, carelessness, and the perfunctory replies of unwilling respondents. To minimise the last, those who wished to abandon the questionnaire after they had had a taste of it were invited to do so. Nevertheless, probing revealed that these errors were not distributed evenly throughout the sample, 26% of them being accounted for by 5.8% of the patients (those excluded from further analysis).

The distribution of many of the scores was negatively skew. This partly results from the fixed-point scale constraining the limits of response. The direction of skew is arbitrary: had we chosen to reverse the order of scoring, it would have been equivalently positive. As a rough estimate of its degree, the distribution of the within-hospital error variance was calculated for each item (Fisher's index ($G1$) -1.2 to $+0.016$; most values around -0.8). This wide range made it impossible to transform to marginal normality, let alone multivariate normality, using any single transformation. A square transformation of all scores, although perhaps a little too fierce, improved the distribution of compound variables, giving for example a normally distributed first principal component (skew: $G1 = -0.14$, $z = 0.92$ NS; kurtosis: $G2 = 3.40$ NS). The skew values of the untransformed compound variables analysed here were, given the relatively large n, within the limits appropriate for univariate analysis as judged by Cochran's (1963) crude index.

The statements were on topics so intrinsically diverse that principal component analysis could not be expected to simplify matters much. Nevertheless, the first principal component was of some interest. The outstanding feature of the 41-variable correlation matrix was that almost all the 820 correlations were positive. This suggests that an individual patient has a general perception of the hospital regime as being satisfactory or otherwise. We tentatively identify the first principal component as this 'satisfaction' variable. Items 16, 21, 20, 2, 38, 40, 30 had the highest correlation with it (r values in descending order, 0.7 to 0.6). These items may provisionally be construed as the patients' perception of their acceptance as people and the preservation of their sense of identity. With the exception of item 19 ('At night the ward is usually quiet'), all the items dealing with material provision fell in the bottom half of the rank-ordered item-component correlations. Using the square-transformed data did not materially affect these inferences. The first principal component derived from an analysis of the patient items accounted for 43.9% of the variance and had the highest correlation ($r = 0.79$) with item 10 ('Some of the patients pester me'). The second principal component (18% of variance) correlated highly ($r = 0.85$) with one item, namely 14 ('Listening to other patients' problems gets me down'), but negligibly with the others.

The patients studied were not a random sample of a large population, so our findings allow no general statement about the experience of patients in psychiatric hospitals. Likewise, comparisons between item scores either singly or in groups allow no generalisation about their relative importance. As with comparisons between different drugs, inferences are tied to dosage, dosage here being wording, and minor changes in wording can, under certain conditions, considerably affect responses (Payne, 1980). The five patient-related items all happened by chance to be worded in the unfavourable form. When the analysis was confined to the statements having this form, neither the sign nor the significance level of the six comparisons were changed. For this group of respondents using these items, the patient-related group evoked the least favourable comment and not merely because their wording was mild; on the contrary, any patient agreeing with these statements was agreeing with strong sentiments. One respondent wrote of a fellow patient cleaning his false teeth at the meal table. On subsequent enquiry, patients spoke of constantly being pestered for money or cigarettes, and of being used as a sounding board for a litany of problems. This last complaint echoes that found by Grad & Sainsbury (1968) in a study of the effects on relatives of patients living at home, although in their survey, it was the patients' self-preoccupation with bodily symptoms which was the most common cause of complaint. The impact of other patients was not found to be significantly related to the respondent's age, sex or whether fellow patients were only of the same sex or included the opposite sex. Nor was there any evidence that tolerance to the habits of fellow patients waxed or waned with time.

On admission patients may bring money with them or subsequently have it brought by relatives or, failing them, social workers. Money means cash (which patients are encouraged to bank) or the means of obtaining it – bank, benefit or pension books. If patients are too ill to make such arrangements, the responsible medical officer is empowered to do so on their behalf. During the period of the study, delays in Hospital 1 were attributable to tardy relatives, to poor communication between administrative and social work staff (now righted) and to a reluctance of the social services department, when agents for benefit for patients living in local authority accommodation, to transfer this agency to the hospital, lest early discharge make it unnecessary.

That the stated preference for ward/sex type accords with actual experience of this type of ward should not lead to any complacent acceptance that patients adapt to their lot. They may merely 'rather bear those ills' they have or, more sanguinely, any general satisfaction with their current ward might find expression in their ward/sex preference.

Our failure to find any relationship between a number of personal and social characteristics and the patients' view of hospital life is a little surprising; nevertheless, it is in keeping with publications from the USA which either find no such relationship or contradictory ones (Weinstein, 1981). Weinstein concludes that here is an exception to the dictum that social factors constitute "meaningful frameworks from which they (the patients) interpret their psychological difficulties and illness-related phenomena". Feelings about hospital life may indeed run too deep to be touched by such influences, but it may be that our methods are too insensitive to detect their effects.

Sensitivity could be increased by better ways of excusing patients who cannot concentrate sufficiently. Life in a psychiatric hospital is an immensely complex experience, and it is probably expecting too much of any single patient to comment on the whole of it. It would be better to break it down into separate topics to be allocated at random to subsets of patients. Twenty questions or statements is probably about right, and would allow expansion of the items devoted to some topics, for instance, the impact of other patients. Since the scores on the items are likely to be intercorrelated, deriving variables from their sums, weighted or otherwise, would further reduce the measurement error problem.

Although the patients' view of hospital life is indispensable, it is not enough. However it is sought, bias arising because of a wish to please cannot be entirely avoided, and our inter-hospital comparison offers only minimal reassurance on this point. There may also be a subtle, or not-so-subtle, pressure to please: patients paint a rosier picture of hospital life before discharge than after. For these reasons, it is best to take our results as a minimum estimate of dissatisfaction. However, even if methods of seeking the patients' view were faultless, they could only be one element in an assessment of the quality of life in a psychiatric hospital. Linn (1969) has raised the melancholy possibility that some patients judge the quality to be good because their only yardstick is an oppressed and threadbare life outside (see also Keith-Spiegel *et al*, 1970), a possibility echoed by one of the patients in this survey, "compared to the suffering world I live well here". For this reason alone, independent appraisal by those leading more privileged lives is an essential complement to the patient's view.

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Appendix

The 45 analysed items of the questionnaire (the nine items not analysed are not included) in ascending order of mean score, showing standard deviation (s.d.), % of unfavourable responses and category coding.

	Item (statement)	*Mean*	*s.d.*[1]	*% of sample giving unfavourable responses*	*Category coding*[2]
1	There have been moments during my stay here when I've been homesick.	2.36	1.09	71	O,N
2	There is such a crowd of people on ward rounds that it is embarrassing to talk about personal problems.	2.85	1.22	43	I
3	I long for more visits from my friends and relatives, at least from some of them.	2.86	1.19	45	O,N
4	I feel lonelier living outside this hospital than I do inside it.	2.87	1.21	45	O,N
5	Enough provision *is* made in this hospital for those wanting peace and quiet.	2.88	1.18	45	M
6	The noise made by other patients gets on my nerves.	2.89	1.07	41	P
7	Compared with my life outside hospital, life in this hospital is quite interesting.	2.92	1.19	39	I

	Item (statement)	*Mean*	*s.d.*[1]	*% of sample giving unfavourable responses*	*Category coding*[2]
8	Some of the patients have disgusting personal habits	2.93	1.08	40	P
9	When I'm in the ward, I feel cooped up.	2.99	1.19	38	I,N
10	Some of the patients pester me.	3.06	1.18	41	P
11	The staff should try harder to stop some of the patients making life difficult for the rest of us.	3.10	1.04	31	P
12	Having been in a psychiatric hospital is going to make it difficult for me to face people outside.	3.14	1.19	38	I,N
13	I'm kept in the dark about the pros and cons of the treatment I'm getting.	3.25	1.09	29	S
14	Listening to other patients' problems gets me down.	3.29	1.04	28	P
15	The ward is sometimes too hot for comfort.	3.30	1.05	28	M
16	There are so many other patients on the ward I feel just one of the herd.	3.37	1.10	26	I
17	I'm given enough say in the treatment I'm having.	3.40	1.06	24	S
18	When you talk to doctors in this hospital, they tend to jump to the wrong conclusions.	3.43	0.95	18	S
19	At night the ward is usually quiet.	3.47	0.99	20	I
20	Some of the medical staff talk down to me.	3.48	1.13	25	S
21	I believe some of the staff feel I am a nuisance.	3.48	1.10	21	S
22	My bed is comfortable.	3.49	1.10	26	M
23	The ward is a draughty place.	3.54	1.06	20	M
24	The hospital is so big I feel swallowed up in it.	3.54	0.95	19	I,N
25	The ward is often too cold for comfort.	3.55	1.06	19	M
26	There is something about this hospital that makes you feel small.	3.56	0.99	17	I
27	Living on a ward with so many other people is embarrassing.	3.57	0.88	14	I
28	Although it's in a hospital, the ward is quite a homely place.	3.57	1.00	19	I
29	I have enough privacy here to attend to my personal needs.	3.59	1.01	19	I
30	The ward seems to belong more to the nurses than to the patients.	3.65	0.98	15	I
31	Because I'm a patient, some of the staff treat me like a second-class citizen.	3.73	1.00	13	S
32	I have enjoyed most of my meals here.	3.78	0.95	11	M
33	Some of the hospital staff are too keen to pry into my private feelings.	3.79	0.91	9	S
34	I feel I can ask the doctors as many questions about my condition as I want.	3.79	0.97	14	S
35	I feel I'm not wanted here.	3.85	1.01	9	S
36	I can have a hot bath/shower as often as I want.	3.85	0.92	13	M
37	I feel I'm treated as an adult here.	3.87	0.84	7	S
38	The staff are, by and large, interested in my point of view.	3.88	0.80	7	S
39	On my arrival at hospital I was made to feel welcome.	3.93	0.92	7	S
40	On the whole, the staff *do* spend enough time with me.	3.97	0.87	7	S
41	During my stay here, I've been kept in nightclothes for far too long.	3.99	0.87	7	
42	The ward is dirty.	4.04	0.82	6	M
43	There are some members of staff who seem genuinely interested in my personal problems.	4.06	0.78	4	S
44	On the whole, the hospital staff are sympathetic.	4.10	0.73	3	S
45	I sometimes have to wait far too long for a ward toilet to become free.	4.12	0.75	3	M

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1. 'Within-hospital' standard deviation
2. Group coding: S = staff attitudes; M = material standards; P = effects of other patients; I = aspects of hospital as an institution; O = other. N refers to those items used as contrasts in the bilinear comparison between hospitals.

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Puerperal Insanity in the 19th and 20th Centuries

ANIS-UR-REHMAN, DAVID ST CLAIR and CHRISTINE PLATZ

All patients with puerperal psychosis admitted to the Royal Edinburgh Hospital within 90 days of childbirth during the periods 1880–90 and 1971–80 were compared. The majority of cases in both groups had an affective illness with an acute presentation and a fixed interval of onset. The 19th-century cases had a more florid presentation and a greater length of admission (mean, 151 days) to the hospital than the 20th-century ones (mean, 39 days). The incidence of the disorder rose from 0.34 per 1000 childbirths per year in the 19th-century group to 1.04 in the 20th-century one, but this could be explained by nosocomial factors. Most 19th-century cases occurred in multigravid women, which questions the association of puerperal psychosis with primiparae.

Although the presentation of psychiatric illness has generally remained unchanged over the past century, the intensity of mental disorders seems to have altered over time (Klaf & Hamilton, 1961; Hare, 1974; Ellard, 1987; Hare, 1988). Cases of delirious mania and catatonic excitement common a century ago are rarely seen now. Furthermore, Loudon (1988) studied patients with puerperal psychosis admitted to Warwick County Lunatic Asylum between 1880 and 1888 and commented on the florid presentation compared with the present day.

It is postulated than an improvement in the general health of the population over the past century has brought about an overall decline in the floridness of mental disorders (Hare, 1974). However, definitive evidence to support this view is lacking. It is hard to compare equivalent patient groups over such a long time epoch since most 19th-century psychiatric classifications differed from contemporary operationalised diagnostic criteria which are based on a Kraepelinian division of psychoses. A rare opportunity for a comparative study on 19th- and 20th-century patients was recently identified at the Royal Edinburgh Hospital. Each patient selected for study was admitted during one of the periods 1880–90 and 1971–80 and had a diagnosis of puerperal mental illness based on contemporary criteria. The changes in symptoms and epidemiology of mental disorders following childbirth could thus be investigated using equivalent groups over a 90 year period.

Method

Subjects

Nineteenth-century cases

Detailed case records of each patient admitted to the Royal Edinburgh Lunatic Asylum are available from 1840 onwards when Dr Mackinnon was Physician Superintendent. The cases used are from the period 1880–90 when it was standard practice to use two parallel diagnostic systems: divisions into mania, melancholia and monomanias similar to contemporary ones, and a second diagnosis based on the classification system by Skae (1863). This system allowed the present study to identify all patients admitted with psychiatric disorder following childbirth since all were labelled as suffering from either 'puerperal' or 'lactational' insanity. A diagnosis of 'puerperal' insanity was given if symptoms occurred within six weeks of delivery. 'Lactational' insanity began after this period or following prolonged lactation.

A systematic search through a full year's admissions during the study period was made to determine whether any patients with mental illness following childbirth had been overlooked by Skae's classification. None was found. Thus, the present study included all women admitted to the Royal Edinburgh Lunatic Asylum with a mental illness within 90 days of delivery from 1880–90. The total number of patients identified was 63. Although there were 38 cases where only approximate dates of childbirth were given in the hospital case notes, a search of birth records at the Scottish Register Office allowed the exact date of delivery to be determined in 28 of these.

Twentieth-century cases

A follow-up study of cases of puerperal psychosis originally studied by Dean & Kendell (1981) was in progress at the Royal Edinburgh Hospital at the time of our investigation and thus we used its findings. In this study, since the hospital served a catchment area of the whole city, computer linkage of obstetric and psychiatric records enabled all women who had received in-patient care at the hospital within 90 days of childbirth to be traced. The total number of cases identified during the period 1971–80 was 108.

Data

Information for both 19th and 20th-century cases, including demographic details, obstetric variables and symptoms, was recorded. Symptoms were identified according to a variety of different criteria. The presence of 'mood swings' required the shifting of mood from elation to depression or vice versa within the first month of admission. 'Confusion' was rated according to the DSM-III (American Psychiatric Association, 1980) criteria for delirium with modifications (Rehman, 1986). Patients were considered to be definitely confused if criteria for any three of the four stems (ABCD) were fulfilled or if there was strong evidence of confusion from clinical records. The coding for 'delusions' was according to the Present State Examination (PSE) glossary of definitions (Wing *et al*, 1974). Furthermore, Research Diagnostic Criteria (RDC) (Spitzer *et al*, 1978) diagnoses were derived for patients in both groups.

The case notes for both the study periods were well recorded. The 19th-century case histories were especially impressive and contained meticulous details about symptoms which facilitated retrospective application of RDC criteria. Quantitative information was obtained by analysis of variance, χ^2 and Fischer's Exact Probability using the Statistical Package for Social Sciences (SPSS, 1983).

Incidence of puerperal psychosis

Figures from the General Register Office for Scotland were obtained in order to ascertain the population and birth rate in Edinburgh for the periods studied. The catchment area for the hospital over both periods was also estimated. Using these data, an approximate estimate of the incidence of puerperal psychoses was made (see Results).

TABLE I
Obstetric features of puerperal patients in the 19th and 20th centuries

Obstetric variables	*19th-century patients (total* n = *63)*	*20th-century patients (total* n = *108)*
Previous pregnancies[1]: number (%)		
primigravidae	14 (31%)	58 (55%)
multigravidae	31 (69%)	48 (45%)*
Mean (s.d.) intervals: days		
Delivery and admission	33 (24)	32 (25)[3]
Delivery and onset of symptoms	16 (26)	17 (21)[3]
Onset of symptoms and admission	21 (28)	16 (17)[3]
Perinatal complications[2]: number (%)		
absent	13 (45%)	55 (60%)
present	16 (55%)	37 (40%)[3]

*$P<0.05$.

1. Information only available for 45 19th- and 106 20th-century patients.
2. Information only available for 29 19th- and 92 20th-century patients.
3. NS.

Results

The mean age of the 63 19th-century cases was 28 (s.d. 5.1) while that of the 108 20th-century patients was 26 (s.d. 5.0) ($P<0.05$). Seventy-four per cent of the 19th-century patients were married as compared with 80% of the 20th-century ones. A past history of mental illness was noted in 18% of the 19th-century group as against 44% of the 20th-century one ($P<0.001$). Twenty-seven per cent of 19th-century patients had a family history of psychiatric illness as opposed to 41% of the 20th-century ones. Interpretation of these results is difficult as they may not have been meticulously recorded in 19th-century patients.

Table I lists the obstetric variables of the two groups. Significantly ($P<0.05$) more 20th-century patients were primigravid compared with 19th-century patients. On the other hand there were no differences between the two groups in the length of time of any of the important obstetric intervals and the onset of symptoms. Similarly, there were no significant differences between the two groups as regards obstetric complications. It should be mentioned, however, that information was not available for all cases, as shown in the table.

Table II lists RDC diagnoses of the two groups. Most cases in both groups had an affective disturbance. There was a preponderance of manic disorder in the 19th-century patients ($P<0.001$). This difference persisted when all cases with elevated mood presenting as part of the illness (i.e. schizophrenic, manic and hypomanic patients) were combined in each group.

Psychotic cases were identified separately in each of the two groups. They were defined as major mental illness with delusions or hallucinations. This comparison removed the dilution effect of admissions for minor psychiatric illness restricted almost entirely to the 20th-century group. The number of psychotic patients in the 19th century was 49

TABLE II
RDC diagnosis of puerperal patients in the 19th and 20th centuries

	19th-century patients (n = 63)	*20th-century patients (n = 108)*
Schizophrenia	2 (3%)	5 (4%)
Schizoaffective disorder		
manic type	4 (6%)	5 (4%)
depressed type	0	3 (3%)
Manic disorder	27 (43%)	15 (14%)*
Hypomanic disorder	0	2 (2%)
Major depressive disorder	23 (36%)	45 (42%)
Minor depressive disorder	1 (2%)	18 (17%)**
Unspecified functional psychosis	1 (2%)	10 (9%)
Organic disorder	5 (8%)	1 (1%)
Personality disorder/ no psychiatric diagnosis	0	4 (4%)

*$P<0.001$.
**$P<0.01$.

TABLE III

Symptoms and outcome of puerperal patients in the 19th and 20th centuries

	19th-century patients (n = 63)	*20th-century patients (n = 108)*
Delusions		
definitely present	45 (71%)	49 (45%)
probably present	7 (11%)	3 (3%)
absent	8 (13%)	56 (52%)*
uncertain	3 (5%)	0
Hallucinations		
definitely present	16 (25%)	24 (22%)
probably present	6 (10%)	4 (4%)
absent	12 (19%)	78 (74%)*
uncertain	29 (46%)	2 (2%)
Motility disturbance		
definitely present	46 (73%)	46 (43%)
probably present	13 (21%)	15 (14%)
absent	4 (6%)	47 (43%)
Confusion		
definitely present	23 (37%)	34 (32%)
probably present	24 (38%)	10 (9%)
absent	16 (25%)	64 (59%)
Length of stay in hospital		
Mean (days)	151.7	39.0*
s.d.	118.8	37.8

*$P<0.001$.

(82%) and in the 20th century, 55 (51%), the difference between the two groups being significant ($P<0.001$).

Table III describes the symptoms and outcome of puerperal mental illness in the two groups. More 19th-century patients were deluded ($P<0.001$). The most common delusions were misinterpretation, misidentification and reference followed by guilt, persecution and expansive ideation. Some examples of 19th-century delusions are as follows: "Believes her baby has been changed for another baby"; "strongly maintains that she is dead and that her husband must die too and they will both go to hell together"; "some people have been burnt on her account"; "she has done wrong and will be burnt alive"; "thought people were going to strip her and hang her"; "believes that her body is all broken into pieces, that she is blocked up, and cannot have any passage from her bowels, that she cannot swallow her food and it does her harm"; "believes that she is being murdered by the inmates of the maternity hospital and that all her relatives have been destroyed"; "devils are constantly following her"; "abuses the nurse and blames her for the war in Egypt"; "imagines she is being drugged with chloroform".

Patients 90 years ago also had more hallucinations ($P<0.001$). These differences remained significant when visual ($P<0.01$) and auditory ($P<0.05$) hallucinations were separately analysed and when psychotic subgroups were compared.

There was similarly a clear excess of patients in the 19th century who had motility disturbance ($P<0.001$) and confusion ($P<0.001$). This also was true for the respective psychotic subgroups ($P<0.05$ and $P<0.001$). No significant differences were found between the two groups as regards mood swings but when the psychotic populations were examined separately, more 19th-century patients had evidence of such disturbance ($P<0.05$). The severity of mood swings was also greater.

Nineteenth-century patients also stayed longer in hospital. This held for the group as a whole ($P<0.001$) as well as the psychotic cases alone ($P<0.001$).

Incidence of puerperal psychosis

The population of Edinburgh which was 414 372 in the period 1880–90, rose to 459 193 in the decade 1971–80, registering a mean increase of 44 821. The mean birth rate for Edinburgh during 1880–90 was 12 982 and during 1971–80 was 5246, a mean decline of 7736 over the study period. No substantial alteration in the size of the catchment area for the Royal Edinburgh Hospital was noted over the 90 year period (Eagles, 1983; Rehman, 1986). The incidence of puerperal admissions to the hospital was calculated during both periods for cases with psychotic illness and found to be 0.34 per 1000 childbirths per year for the 19th century and 1.04 for the 20th century.

Discussion

This study shows that puerperal psychosis in the 19th century is similar to that of today in that most cases have an affective disorder, the period of onset is a fixed interval after childbirth and the presentation is manic. In addition to this similarity, several factors are not significant for both 19th- and 20th-century cases. The proportion of unmarried mothers in both groups is essentially the same which mitigates against an explanation based on social rejection or stigma. Furthermore, no significant association has been shown, now or then, with obstetric complications. The results do not lend support to the evidence that post-partum psychosis is an illness of primigravid women (Thomas & Gordon, 1959; Kendell, 1981; Kendell *et al*, 1987). In the 19th-century cohorts most cases occurred in multigravid women which relates to the fact that, at this time, most pregnancies occurred in such women.

Certain differences have been highlighted however between 19th- and 20th-century puerperal psychosis patients. The former showed a more florid presentation, similar to that observed by Loudon (1988) over the same period. They also had more numerous symptoms. Moreover, this excess morbidity could not be wholly attributed to organic causes. Visual hallucinations which are seldom present now in functional illness were mainly seen in 19th-century patients in whom an organic illness had most probably been excluded. Some of the 19th-century clinical descriptions are given in the appendix.

The more florid 19th-century presentation could however be mainly due to nosocomial factors. Nowadays neuroleptics are commonly given to patients on admission and quite often before what is misleadingly called the 'initial mental state' has completely finished. This could have affected the results of this study, as the RDC diagnoses were based on all the information contained in the case notes during the first month of admission to hospital. Certainly the introduction of electroconvulsive therapy (ECT) and neuroleptic drugs has shortened the duration of the illness and the length of admission. The 19-century figures could therefore correspond to the pre-drug, pre-ECT era and represent the natural history of the disorder. Jansson (1964) and Prothero (1969) clearly showed that with introduction of modern treatments the duration and outcome of post-natal illness considerably improved.

As the risk of developing puerperal psychosis is dependent on childbirth, it could be expected that the greater the number of episodes of childbirth, the greater would be the risk of the illness. Although data from the General Register for Scotland showed that despite the fall in the birth rate, the admission rate for puerperal illness per birth event had almost tripled over the study period, this rise in incidence needs to be put into the context of Clouston's (1886) figures for Edinburgh which show a much higher incidence for the 19th century (1 in 400 labours) than our study did.

The low incidence in the 19th century noted in this study could be due to several reasons. There were fewer admissions of psychotic patients then to the Royal Edinburgh Asylum, a trend reflected in all psychiatric hospitals in Scotland (Cameron, 1954; Rehman, 1986). By contrast, now there are more in-patient facilities and liberal admission policies and an increased readiness by the public for in-patient care. Furthermore, it is possible that in the 19th century some patients who also had severe puerperal infection would have died before being admitted to hospital and other patients would have been treated at home, particularly if good social supports were available (Clouston quoted a figure of 9% for such cases; Clouston, 1886; Thompson, 1984).

All 19th-century patients required compulsory detention for in-patient psychiatric treatment. Adequate grounds for certification necessitated the presence of signs of insanity and this could have resulted in over-reporting of psychotic cases and manic patients in the present study. Furthermore, although strict catchment areas now make it reasonable to draw inferences on the incidence based on modern statistics, the possibility of admission to private nursing homes and asylums in the 19th century, especially in milder cases, cannot be ruled out.

Although the large discrepancy in puerperal psychotic admissions over the past century can be mostly explained by the above reasons, the possibility of change in severity of illness cannot be fully excluded. Several supposed risk factors could have operated in combination to cause a more florid illness in the 19th century. Genetic vulnerability, poor nutrition and pre-natal damage to the mother herself at the time of her own birth are some of the factors which need consideration.

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Appendix

Case 1

Mrs X, a housewife living in 11 Falem Place, Edinburgh, was admitted to Royal Edinburgh Asylum on 12 June 1883 with melancholia following the normal birth of a healthy baby whom she did not nurse. She had had two previous admissions to the Asylum for depression. Her admission was under a compulsory medical certificate as she was restless, perturbed, sleepless, had a poor appetite and had made desperate attempts to kill herself by throwing herself out of a window.

She felt despondent and cried, saying that there was "a mist of darkness before her which she couldn't get through". On mental state examination she was found to be very sad and tearful with frank suicidal ideation. Her speech was coherent and there was no evidence of delusions or hallucinations. A physical examination found her to be thin, pale, weak and "respectable with brown hair and grey eyes". She had "a weak physique due to poor muscularity and fatness". No evidence of an organic illness was found and her temperature was normal.

During her stay in the hospital she gradually improved with plenty of food and exercise and by 1 September 1883 was cheerful, in good health and anxious to return home. She was therefore discharged. Unfortunately the same month she committed suicide by jumping over the Edinburgh Dean bridge into the stream below. This was reported in *The Scotsman*.

Case 2

Mrs Y, a 33-year-old Protestant housewife, was admitted from Haddington as a private patient on 31 December 1885, with acute puerperal mania. She had given birth to a son four weeks earlier following an easy and normal labour.

She nursed the child until a week prior to her admission when she became ill. There was no previous history or family history of mental illness.

On admission her mood was generally elated and she was restless, excited and sleepless. She talked nonsense incessantly and was very noisy. She had delusions that her child had been changed and that people were hiding in the house and were threatening her. She also believed that she had no husband and that she got her child from "the Lord on a dark night".

She was removed to a padded cell and given paraldehyde and potassium bromide. By 4 May 1886 she had become "quite coherent and rationale and was most industrious but had still a morbid degree of elevation of mood". By 15 May 1886, she was found to "quite sane in all respects" and was sent home on pass. She was discharged on 31 May 1886 when she had fully recovered.

Case 3

Mrs Z, a 31-year-old housewife from 8, Gibson Terrace, Edinburgh, was admitted on 14 March 1881 to the Asylum with a melancholic illness. There was no past or family history of psychiatric illness. She had given birth to a child on 17 February 1881 and her labour was "natural and speedy".

She was profusely depressed and constantly moaned and cried. She thought she was lost. There was considerable motor restlessness with wringing and clasping of hands. She kept screaming "Oh! the suicide" and had to be restrained to prevent her from committing suicide. Her sleep and appetite were poor. She believed that by her own obstinacy she had committed some terrible crime, that God was to punish her and would never forgive her. She said that there was no hope for her and that she must go to hell. Her memory was poor as to recent events and she was not quite sure when her baby was born.

On physical examination she weighed 8 stone 13 pounds, her "fatness was poor and her muscularity was small". There was no evidence of physical disease except that she appeared anaemic.

She was given two custards, extra milk, 6 ounces of sherry, a pint of porter, a tonic (Ferri dialysat), potassium bromide (45 g) and chloral (20 g).

By 22 June 1881 Mrs Z had steadily improved and had been allowed occasional passes to go home for a day. She was discharged as 'recovered'.

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Self-poisoning in Adolescents
Hospital Admissions and Deaths in the Oxford Region 1980–85

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Linked hospital and death records for 10–20-year-olds admitted with a diagnosis of poisoning were analysed. Between 1980 and 1985 there was a significant decline in admission rates, which was mainly attributable to a decline among 16–20-year-old females. There was no evidence of a decline in the admission rates among 12–15-year-olds. Ten per cent of the study population had at least one further hospital admission for poisoning during the mean follow-up period of 3.6 years. Female admission rates were substantially higher than those in males but readmission rates, given a first admission, were similar. The death rate in the study cohort was significantly higher than would be expected in the general population of this age and nearly all the deaths were from violent or unnatural causes.

Self-poisoning is one of the commonest reasons for hospital admission in adolescents. Previous studies of people aged 12–20 years in the Oxford region (Hawton & Goldacre, 1982; Goldacre & Hawton, 1985) indicated that admission rates for self-poisoning increased during the 1970s, as they did nationally, and showed that the average annual death rate in the few years after discharge from hospital after an episode of self-poisoning was approximately four times higher than the national average annual death rate in the same age group. Suicide was the main reason for death in self-poisoners.

This paper reports the findings of a study undertaken in the Oxford region to provide updated information about trends in admission rates for self-poisoning in adolescents. The aims of the study were to determine whether the general decline in admission rates seen since the late 1970s (Brewer & Farmer, 1985) has been experienced by adolescents, to study whether the age at which self-poisoning becomes common has changed, and to use record linkage to examine the contemporary profile of repetition rates and mortality rates among self-poisoners.

Method

Oxford Record Linkage Study

The Oxford Record Linkage Study (Goldacre *et al*, 1988) was used to analyse data on hospital admissions for self-poisoning in people aged 12–20 years. The study contains abstracts of records of hospital admissions and death. As these records can be linked, it was possible to study the pattern of repeat episodes and subsequent death for individuals following an initial admission.

In the period covered by this report, data were collected in six districts of the Oxford region with a total population of two million people, including approximately 390 000 people aged 10–20 years.

Identification of episodes of poisoning

Episodes of poisoning were identified using ICD–9 codes for "poisoning by drugs and medicaments" (codes 960–977). These categories include deliberate self-poisoning and overdoses of substances taken in error, but "exclude the adverse effects of correct substances properly administered" (World Health Organization, 1978). Although episodes other than deliberate self-poisoning are therefore covered by these codes, hospital admissions in these categories for reasons other than deliberate self-poisoning are in fact very uncommon in teenagers. We were able to verify this in a sample of patients, as in our previous study (Hawton & Goldacre, 1982). Of 1123 records for poisoning in our sample, 1065 (95%) were confirmed as deliberate self-poisoning. Routine data on hospital admissions for poisoning coded in ICD–9 categories 960–977 therefore represent a good proxy for large-scale investigations of self-poisoning in this age group.

Data were analysed for general hospital admissions of individuals aged 10–20 years who had a main discharge diagnosis of poisoning between 1980 and 1985. Counts of admissions from 1974 to 1979 were also recorded, for comparison. Most of the results reported here are confined to the 12–20 year age group because, as we report below, poisoning was very uncommon in 10- and 11-year-olds. Trends in admission rates were analysed using the χ^2 test for trend in proportions (Armitage & Berry, 1987).

Repetition and deaths

Each patient's first recorded episode of poisoning in 1980–84 was defined as an index admission. Any subsequent admissions for poisoning, and any deaths, up to the end of 1985 were identified by record linkage. Each person was followed by this means for a minimum of one and a maximum of six years (mean 3.6 years). Any hospital admissions outside the Oxford Record Linkage Study area are not recorded in the system. However, deaths of people resident within the area but which occur outside it are recorded. Any further episodes of poisoning and deaths which occurred in those who became over 20 years of age during 1980–85 were included in the analysis.

The number of deaths in the study cohort was compared with the number of expected deaths in a population of this age and size. The expected number of deaths was calculated by applying death rates in this age group in the Oxford region for the years of the study to the number of people in each age group in our cohort.

Deaths from poisoning without prior record of hospital admission

All deaths from poisoning, whether as the underlying or a contributing cause, among people aged 12–20 years between 1980 and 1985 in the study region were recorded. These included individuals who died without prior recorded hospital admission for self-poisoning. Any other hospital records on the Oxford Record Linkage Study files for these patients were also identified.

Results

Admission rates by age group, sex, and year

There were 4007 admissions to hospital for poisoning between 1980 and 1985 in the 10–20-year age group. This comprised 3.4% of all admissions to general hospitals in this age group during the period. Only 36 of these episodes were for people aged 10 or 11 years. Between 1980 and 1985 the hospital admission rates for poisoning in 12–20-year-olds showed a small but statistically significant decline (Table I). The major component of the decline was that in admission rates in 16–20-year-old females.

Figure 1 shows that the decline in admission rates in the older adolescents began in 1978, after a peak in 1977. In the younger age group the rates remained more stable, although the trend in the most recent years was, if anything, upwards.

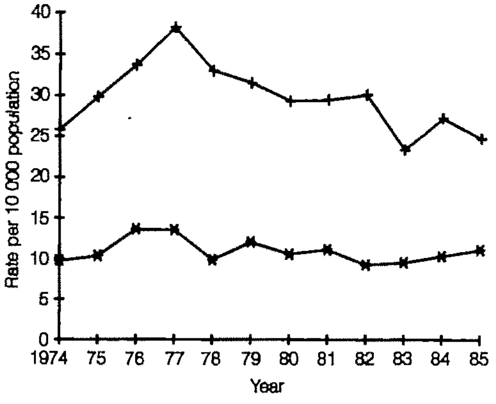

FIG. 1. Hospital admission rates 1974–85 by age group (**12–15 years, + + 16–20 years) for poisoning by drug and medicaments.

Figure 2 shows admission rates at each single year of age and compares data for 1980–85 with that previously reported for 1974–79 (Hawton & Goldacre, 1982). The figure shows that admission rates increase strikingly with age from 12 years. There was no change in the age at which self-poisoning rates increased in the later period; nor was there any evidence of changes in the age profile for either sex between the two study periods. Admission rates for girls were four times higher than for boys in the 12–15-year age group and were more than double those for boys in the 16–20-year age group.

Medicinal agents

The group of agents coded under ICD–9 code 965 (analgesics, antipyretics, antirheumatics) accounted for 50% of all episodes between 1980 and 1985, with drugs acting

TABLE I

Hospital admission rates by age group and sex for poisoning by drugs and medicaments

Age group			*Rate per 10 000 age/sex group*						
		(n)[1]	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	χ^2 *trend*[2]
12–20 years	All events	662	21.1	21.6	21.3	17.7	20.3	19.3	6.5*
12–15 years	Males	27	4.6	4.0	3.2	3.2	3.0	4.3	0.7
	Females	115	16.9	18.7	15.6	16.2	18.2	18.6	0.3
	All	141	10.5	11.1	9.2	9.5	10.3	11.1	0.0
16–20 years	Males	163	18.1	16.5	17.4	13.3	16.9	14.9	3.0
	Females	358	42.0	44.0	44.2	34.7	39.0	36.0	9.5**
	All	521	29.3	29.5	30.1	23.4	27.3	24.8	12.7**
Drugs acting on central nervous system only[3]									
12–15 years	Males	9	1.6	1.5	1.0	1.0	1.1	1.0	1.4
	Females	25	5.0	3.7	2.7	3.2	4.3	3.5	0.7
16–20 years	Males	42	4.9	4.4	4.8	3.7	3.8	3.1	4.8*
	Females	93	12.0	12.9	12.0	8.5	8.1	8.8	14.4**

1. Average annual number of admissions (for individuals admitted more than once, each admission is counted in this table).
2. χ^2 for trend over 1980–85 in each age/sex group.
3. ICD–9 codes 966–970, principally psychotropics (code 969).

*$P<0.05$, **$P<0.01$.

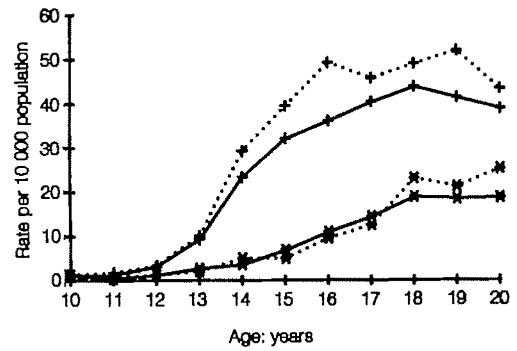

FIG. 2. Average annual rate of hospital admissions 1974–79 (····) and 1980–85 (——) for poisoning by drugs and medicaments by age and sex (+ – + females, ×–× males).

on the central nervous system (codes 966–970), principally psychotropics (code 969), comprising 25% of episodes (Table I). The principal change over time was that there was an overall decline in the number of admissions ascribed to poisoning with psychotropic agents. There was no appreciable change in the use of analgesics or other drugs.

Repetition

Of the 3034 individuals aged 12–20 years who had an index admission between 1980 and 1984, 2152 (71%) were female. Two of the index admissions for boys resulted in their deaths. These two index admissions were excluded from the analysis of repetition rates.

Two hundred and one people (6.6%) had at least one further hospital admission for poisoning within a year after their index admission (Table II). Repetition rates were slightly higher overall in females than males (10.5% and 9.3%, respectively). However, males who had a further admission within one year of their index admission were more likely to be admitted within the first three months (57.4%) than were females (42.9%). Repetition rates were slightly higher in 16–20-year-olds than 12–15-year-olds among those who had a further admission within one year of their index admission (6.9% in older adolescents, 5.8% in younger adolescents). None of these differences were statistically significant. In all, 309 individuals (10.2%) were admitted again for poisoning at least once in the mean follow-up of 3.6 years. The decrease in the proportion of individuals who had a further admission for poisoning within one year of index admission was not significant, and the pattern of repetition was very similar to that reported for the 1970s (Goldacre & Hawton, 1985).

Among those who were 12–15 years old at index admission, none of the boys had more than two admissions for poisoning, but 12 (2.2%) of the girls had three or more admissions for poisoning. Of the 2374 16–20-year-olds, 76 (3.2%) had at least three admissions for poisoning during the study period. The highest number of admissions for poisoning was 14, by a female who was 15 years old at her index admission in 1983.

Deaths following prior admission for self poisoning

Sixteen people in the self-poisoning cohort died. Two males died at index admission and 14 (9 males, 5 females) died during the follow-up. Of these 14, 13 were between 16 and 20 years of age at their index admission and all but one were aged 19 years or over at the time of death. Seven of the 14 deaths occurred within a year of an admission. Only two of those who died had more than one recorded hospital admission for self-poisoning.

The two individuals who died at index admission had coroners' verdicts of suicide. Three of the other 14 also had verdicts of suicide on their death certificates (one male who died from a gunshot wound, another male who died from self-poisoning, and a girl who jumped from a building).

Two of the other 11 deaths were from natural causes, both respiratory deaths in females, and there was no inquest. The remaining nine, seven males and two females, died 'violent' or unnatural deaths (e.g. hanging, drowning, multiple injuries on a railway line, road traffic accidents) but had verdicts recorded other than suicide.

The average annual death rates of those discharged alive after an admission for self-poisoning were 0.6 and 2.8 per 1000 females and males, respectively. The rate for males is significantly higher than the corresponding rate, of 0.8 per 1000 males, in the general population of similar age (Table III).

TABLE II

Number and cumulative percentage of individuals who had at least one further admission for poisoning by length of time to second admission and year of index admission

Year	*No. of index admissions*	*Number of months to first repeat (cumulative %)*				
		0–11	*12–23*	*24–35*	*36–47*	*48 or more*
1980	640	52 (8.1)	21 (11.4)	13 (13.4)	7 (14.5)	7 (15.6)
1981	634	44 (6.9)	11 (8.7)	5 (9.5)	3 (9.9)	0 (9.9)
1982	634	36 (5.7)	7 (6.8)	8 (8.0)	1 (8.2)	–
1983	521	36 (6.9)	11 (9.0)	4 (9.8)	–	–
1984	603	33 (5.5)	10 (7.1)	–	–	–
Total	3032	201 (6.6)[1]	60 (8.6)	30 (9.6)	11 (10.0)	7 (10.2)[2]

1. χ^2 trend = 3.0, not significant.
2. Mean follow-up period of 3.6 years.

TABLE III

Number of deaths during follow-up in the study population compared with the expected number of deaths for the same age group in the general population

	Observed	*Expected*[1]	χ^2	*Observed/ expected*	*95% confidence interval*[2]
Persons	14	4.8	17.6*	2.9	1.4–4.4
Males	9	2.5	16.9*	3.6	1.2–6.0
Females	5	2.3	3.2	2.2	0.3–4.1

1. Based on deaths for all causes in the Oxford Regional Health Authority area.
2. Estimated using $\sqrt{O}/E$.
*$P<0.01$.

Death from poisoning without prior admission for poisoning

In the same period, 1980–85, ten other people resident in the study region aged 12–20 years died from poisoning by medicinal agents. There was no record of hospital admission for poisoning before their death. Using accepted criteria for obtaining an accurate estimate of the number of suicides by including cases with coroners' verdicts of open verdict and accidental death due to poisoning (Adelstein & Mardon, 1975), it is likely that nine of these deaths were suicides.

Discussion

This study has only covered self-poisoning that resulted in hospital admission or death. It is conceivable that the overall pattern of self-poisoning, including non-fatal cases not admitted to hospital, is different from that reported here. For example, there could have been differences in the characteristics of self-poisoners who were admitted to hospital and those who were not (Owens & Jones, 1988) or changes over time in the proportion of patients presenting at accident and emergency departments who were admitted to hospital (Gardner, 1980). However, at the John Radcliffe Hospital in Oxford there has been no appreciable change over the years covered by this study in this proportion (approximately 88%). If this applies across the region, it indicates that the decline in admissions for self-poisoning in older female adolescents has arisen as a result of a reduction in self-poisoning.

The first recorded admission for poisoning in our data may not have been an individual's first-ever admission for poisoning. A previous admission may have occurred outside the Oxford Record Linkage Study area, in an earlier year, or at a younger age, although the latter is unusual. We also could not identify migration of patients into or out of the Oxford region on an individual basis. Using data from the Office of Population Censuses and Surveys (1986) on movements between family practitioner committees in England and Wales it was possible to estimate that, in aggregate, about 4% of 15–24-year-olds move out of the Oxford region each year. Making an adjustment for this in the older adolescents would indicate that 7.2% of 16–20-year-olds repeat within a year, rather than 6.9%.

Brewer & Farmer (1985) have suggested that the recent reduction in self-poisoning reflects changes in the availability of prescribed sedatives and other psychoactive drugs. In our study the decline in overall admission rates for poisoning has been most strikingly seen in admissions for poisoning using psychotropic-type substances. This could suggest that general practitioners are now more careful in their prescribing of psychotropics (the majority of which will be benzodiazepines).

This result is similar to the result of a study of parasuicide in all age groups admitted to the John Radcliffe Hospital in Oxford (Platt *et al*, 1988), where there was a reduction in the use of barbiturates and minor tranquillisers. In the study by Platt *et al*, there was evidence that this reduction was offset by the increased use of paracetamol. In our study of the Oxford region as a whole we found no increase overall in the use of analgesics or other drugs in the adolescent age group.

In contrast to recent trends in other age groups, admission rates for self-poisoning in young adolescents have not declined. This emphasises the need for general hospital services for self-poisoning patients to maintain close liaison with local child and adolescent services as recommended in guidelines from the Department of Health & Social Security (1984).

Comparing the 1970s and 1980s data there has been no reduction in the age at which self-poisoning becomes common. Repetition rates were similar in this study to those in the earlier study and remain relatively high: 6.6% of individuals had a second admission within a year of their first admission for poisoning.

The risk of death was greater among older adolescents, particularly males. A minority of the deaths had a coroner's verdict of suicide recorded but the violent nature of some of the other deaths suggests that possibly more could have been of suicidal intent. Clinicians need to be especially vigilant for suicide risk in older adolescent and young adult males.

Deaths among male adolescents after admission for poisoning have remained significantly higher than in the general population of the same age group. Nonetheless, most deaths occurred in people with few or no previous recorded admissions for self-poisoning. Thus, clinicians should note that, unlike in adults (Hawton & Fagg, 1988), having more than one admission for self-poisoning may not be a good predictor of death. This may be because of effective support and counselling on first admission. It is also possible that there are two populations of self-poisoners: those at high risk of death, and those who have more than one admission for self-poisoning but who are not intent on taking their own lives. Further research is needed to identify the characteristics of self-poisoners who eventually commit suicide, to determine whether ways can be found to reduce this waste of young lives.

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A Structured Programme for Out-patient Alcohol Detoxification

MARK N. COLLINS, TOM BURNS, PETER A. H. VAN DEN BERK and GARY F. TUBMAN

An out-patient alcohol detoxification service based in a psychiatric emergency clinic is described. Of 173 patients referred during the first year, 76 (44%) were accepted for the programme; 60 (79%) of these successfully completed detoxification with no medical complications. Compared with previous years, during the year of operation of the service there was a 50% fall in the number of in-patient admissions for detoxification to the local hospital. We conclude that a structured out-patient detoxification programme is safe and effective, and may obviate the need for many patients to be admitted, freeing psychiatric beds for other uses.

The medical management of patients who are dependent on alcohol and who present with a request to be 'dried out' is often haphazard. In some cases they will be admitted to hospital, either to a general psychiatric or, sometimes, a general medical ward. They may be referred to a specialist alcohol unit where such a unit is prepared to assess patients on a 'demand' basis, or they may be referred to their general practitioner (GP). The economic and social consequences of admission to hospital are enormous, but surprisingly few studies of out-patient detoxification have been performed in the UK.

Out-patient detoxification is widespread in Scandinavia (Alsen, 1975; Bjorkqvist *et al*, 1976) and has been described in detail in the USA (Feldman *et al*, 1975; Stinnett, 1982), with results suggesting it is both safe and, in the short term, effective. Webb & Unwin (1988) studied 50 patients treated at the unit originally described by Stinnett (1982) and attempted to identify predictive factors for successful out-patient treatment. At the Maudsley Hospital Emergency Clinic in London, 10.2% of attendances over six months had alcohol or drug problems (Lim, 1983). Out-patient detoxification is offered to attenders at this clinic, and outcome in a group of 26 patients seen consecutively over a month has been described (Drummond & Chalmers, 1986). GPs probably supervise detoxification of alcoholic patients quite frequently: a postal questionnaire sent to all GPs in the Exeter health district estimated that approximately half of all patients seen in the practices with alcohol dependence were managed at home (Stockwell *et al*, 1986).

We identified the need for a service offering out-patient detoxification with medical supervision and structured counselling for patients with alcohol dependence; we intended to provide an alternative means of treatment for those patients who might otherwise have been admitted to hospital, but did not see the service as addressing longer-term management issues. The purpose of this paper is to describe the programme, the results of the first year of operation, and to speculate on the effects this might have on in-patient services.

Method

The service was provided from the Psychiatric Emergency Clinic of St George's Hospital, London. The clinic is open Monday to Friday, 9 a.m. to 5 p.m., and accepts referrals, from any source, of patients from the appropriate catchment area of Wandsworth and Merton health districts; self-referrals, although not encouraged, are seen. The clinic is staffed by two trained nurses, who see all referrals and where necessary seek the opinion of a psychiatric registrar on site. Back-up medical cover is provided by a senior registrar and consultant psychiatrist.

Patients referred for out-patient alcohol detoxification are first interviewed by the nurse who takes a full history, including a detailed drinking history, and assesses their suitability for the programme. Criteria for acceptance are that the patients are aged 18–70, from the appropriate catchment area, fulfilling the requirements for a diagnosis of alcohol-dependence syndrome and with an expressed inability to detoxify themselves without assistance. Those abusing substances other than alcohol are excluded, and patients must be physically capable of attending the emergency clinic on a daily basis. If delirium tremens is present or thought to be imminent, the patient is referred for in-patient treatment. Each patient completes the Severity of Alcohol Dependence Questionnaire (SADQ; Stockwell *et al*, 1979; 1983). Physical and mental state examinations are performed by the duty registrar, and blood taken for full blood count, analysis of urea and electrolytes, blood sugar level, and liver function tests.

If accepted, a patient is given a starting date which is usually the next working day, although no patient starts on a Friday; those patients who have already stopped drinking may start on the day of assessment. A typewritten hand-out explaining the details of the programme is given to the patient and a relative where appropriate. A condition of treatment is that patients submit to a daily breath alcohol measurement, and if there is any evidence of alcohol consumption during the programme, then treatment is immediately terminated; this point is emphasised in the hand-out and reinforced verbally.

For the purposes of detoxification the patient is assigned to either a severely dependent or a moderately dependent group, depending on drinking history and SADQ score. The SADQ is a 20-item self-completion questionnaire in which the previous month's drinking is considered and items rated on a four-point frequency scale (0–3) ranging from 'almost never' (0) to 'nearly always' (3) (total possible score range 0–60). A score of 30 or less indicates mild to moderate dependence, while a score of 31 or more indicates severe dependence.

We chose diazepam as the detoxification agent. A plethora of drugs have been used over the years with various advantages and disadvantages (Butler & Messiha, 1986; Naranjo & Sellers, 1986) but benzodiazepines are probably the safest and most established; in particular, there have been reports of potential problems with chlormethiazole (McInnes, 1987) which is widely used in the UK. Table I displays the dosage schedules for the two groups. Patients were given 5 mg tablets and instructed in how to divide the doses appropriately. Most patients took the pills three or four times daily, but a few took them up to six times daily. Adjustments could be made on the second day depending on observed or reported oversedation or breakthrough withdrawal symptoms, but in practice this happened rarely.

Patients also received oral thiamine (100 mg daily). Medication was dispensed on a daily basis, no more than 24 hours' supply being given at a time. At weekends, where necessary, arrangements were made for the patient to collect medication from the local hospital casualty department or the nearest psychiatric hospital.

As well as medication, each patient received five sessions of counselling (30–45 minutes each) on consecutive working days with the same nurse who performed the initial assessment. The content of each session is partly structured and we identified specific issues to be addressed with every patient, a check-list being provided to ensure that each has been covered. The broad content of sessions is as follows.

(a) The first session is chiefly assessment, with an emphasis on ascertaining the patient's particular physical, mental, emotional, financial, work-related and relationship problems. The week's programme is explained in detail and the patient encouraged to ventilate fears about detoxification.

(b) In the second session the programme is recapitulated and further assessment made of immediate problems, particularly physical health. Any other worries are discussed. Health education is provided, focusing on evidence of what damage alcohol has done to the patient, combined with more general risks.

(c) The third session deals with issues arising from the previous sessions. There is specific discussion of identified problems in the various areas of patients' lives, with attempts at finding alternative coping strategies. Further health education is given.

(d) The fourth session is similar to the third session, with more emphasis on what longer-term changes need to be made now that the patient is beginning to feel better physically.

(e) In the fifth session, there is detailed discussion of long-term support including groups such as Alcoholics Anonymous, Accept and Turning Point (information leaflets and telephone numbers are given). Feedback is given to patients on how their problems appear to the counsellor, particularly emphasising the achievement of detoxification.

Throughout, the emphasis is on a supportive approach, with practical solutions to individual problems being sought. Direct confrontation is avoided except on the issue of drinking during the programme; the fact that a breathalyser is routinely used at every visit makes this paradoxically non-threatening. Responsibility for maintaining sobriety is placed firmly in the patients' hands, and they are expected to telephone at least one voluntary agency. Where appropriate, medical follow-up is arranged.

The final part of the study was designed to see if there was any indication of the effect this service might have on numbers of patients treated in hospital. All patients from the appropriate catchment area are admitted to one psychiatric hospital. Records are kept on file of all admissions, with a discharge diagnosis and brief indication of the problem and management. It is thus possible to identify all patients admitted with a diagnosis of alcohol-dependence syndrome where the purpose of admission was alcohol detoxification. Information on such admissions was recorded for the four years preceding the start of the out-patient service, and for the year of the out-patient service.

TABLE I
Medication regimes for patients severely and moderately dependent on alcohol

	Total daily dose diazepam: mg	
Day	*Severely dependent*	*Moderately dependent*
1	40	30
2	40*	30*
3	30	20
4	20	10
5	15	5
6	10	—
7	5	—

*The dose on day 2 may be varied according to observed and reported symptoms in the previous 24 hours.

TABLE II
Immediate management of all referred for assessment for out-patient detoxification

Management	n	%
Accepted for programme	76	(44)
Psychiatric admission	8	(5)
Medical admission	6	(3)
Referred to specialist alcohol unit	9	(5)
Referred to psychiatric out-patients	19	(11)
Referred back to GP	20	(12)
Referred to social worker	2	(1)
Referred to voluntary agency (e.g. AA, Accept)	22	(13)
Referred for housing assistance	11	(6)

Results

Between 1 August 1987 and 31 July 1988, 173 patients were referred for assessment for out-patient detoxification. As one might predict, 135 (78%) were male and 105 (61%) were single or separated; 149 (86%) were aged between 26 and 55. A total of 97 of the 173 patients were not referred for out-patient detoxification (Table II). Sixty-nine were not physically dependent, while five were too drunk to be assessed and failed to return sober for assessments subsequently. A further six had medical complications of sufficient severity to warrant medical admission: these included two cases of severe jaundice, three of active delirium tremens with pyrexia and one of withdrawal fits. Eight patients were admitted to a psychiatric hospital: five categorically refused to consider attempting the out-patient programme, and three were thought unsuitable because of a combination of physical frailty, social isolation, and geographical distance from the clinic. Nine patients were under the active care of specialist alcohol units or hospitals outside our catchment area and were referred to their local services.

Of the 76 (44%) referred, 69 (91%) had an SADQ score of greater than 30, indicating severe dependence.

Our only measure of outcome was successful completion of detoxification; we made no attempt in this study to perform longer-term follow-up. Thus success was defined as attending all sessions, giving no history of alcohol consumption and having negative breathalyser results at all sessions after assessment. Sixty (79%) of those accepted for the programme successfully completed detoxification. There were no significant medical complications such as fits or delirium tremens in the successful group, and diazepam dosage was satisfactory in all but three patients, in whom minor adjustments were made on the second day. Of the 16 patients who failed to complete, eight continued to drink, while the other eight failed to attend. Although we did no more than inform the GPs of their failure, we know that none were admitted to the local general medical or psychiatric hospital at the time of their failed attendances.

Table III shows the numbers of patients with alcohol-dependence syndrome who were admitted to general adult psychiatric catchment area wards of the local mental hospital for each year from August 1983 to July 1988 for detoxification.

TABLE III
Number of patients admitted for in-patient detoxification

	n
August 1983–July 1984	104
August 1984–July 1985	106
August 1985–July 1986	105
August 1986–July 1987	117
August 1987–July 1988 (out-patient service operating)	52

Discussion

Our clinical experience suggests that out-patient detoxification is safe and effective for a group of alcoholic patients who might otherwise be admitted to hospital for want of out-patient resources. The financial implications of this are obvious.

Although only 44% of those presenting were in fact accepted for the programme, this figure is similar to that from other centres (Feldman *et al*, 1975). The reasons for rejection were more often social or bureaucratic than medical. Our basic data do not suggest that the group of patients accepted was particularly different from other reported groups. The vast majority were severely dependent on alcohol as judged by the SADQ, a widely accepted instrument of assessment.

The structure of the counselling sessions was concrete and practical; nursing staff who took the sessions found it helpful to have a check-list of areas to be covered. While we did not attempt to measure this, it was our impression, supported by spontaneous comments from experienced patients, that out-patients probably received more attention than in-patient alcoholics would have received on busy wards where overstretched nurses were more likely to be devoting their time to disturbed psychotic patients.

The diazepam detoxification regime was effective. While the choice of detoxification agent is the subject of debate (Naranjo & Sellers, 1986), we experienced no serious problems of breakthrough withdrawal or oversedation with diazepam. Even with the relatively rigid format of two fixed-dose regimes, only two patients required a 10 mg increase in dose on the second day, and one patient a 10 mg decrease. We cannot of course be certain that those patients failing to complete the programme suffered no medical complications, but suspect this to be unlikely, since they most probably would have been in contact with their GPs or local hospital if they were physically ill.

That 79% of patients accepted for the programme were able to complete it successfully indicates that it is achieving its desired effect. This figure is similar to the results of Feldman *et al* (1975), but better than results of Stinnett (1982) and of Drummond & Chalmers (1986): the latter may well have been dealing with a more socially vulnerable group of patients. Obviously detoxification is only the first step in the process of recovery from alcoholism. It is still unclear, however, whether elaborate long-term treatment is more effective than a single initial intervention in some alcoholic patients (Edwards *et al*, 1977). There are no particular reasons why out-patient detoxification should have any greater or lesser effect on long-term outcome than in-patient treatment. The only way to resolve this would be by a study using random allocation to in-patient and out-patient groups, with long-term follow-up of both.

Perhaps the most striking finding of our study is the dramatic fall (50%) in the number of patients admitted to the local hospital for detoxification during the first year of the out-patient service, compared with previous years (Table III). This indicates a potential saving of at least 74 in-patient weeks (assuming an average stay of ten days). Of course, there are several alternative explanations for our findings. There may have been a 'novelty value' attached to our service, other alcohol services may have been set up in the district without our knowledge, or this may have represented a chance swing. However, our service was not promoted beyond a letter informing colleagues of its existence, with no suggestion that it should be used in preference to other treatments. No new acute treatment facilities were notified to the district alcohol services co-ordinator. The fall in admissions was dramatic, without any suggestion of a declining trend over the preceding years. We therefore suggest that these figures lend strong support to the idea that the out-patient service is treating patients who would otherwise have been admitted to hospital.

Given the low cost of out-patient treatment compared with admission, the simplicity of administration of the programme by, in the main, nursing rather than medical staff, and its apparent safety, we would encourage others to consider setting up such services, allowing further research into longer-term efficacy. While our service is based in a psychiatric emergency clinic, there seems to be no reason why similar services should not operate out of general accident and emergency departments or general practice surgeries involving the practice nurse.

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The Effect of Moderate Weight Loss on Overnight Melatonin Secretion

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Overnight plasma melatonin level was measured in ten healthy women before and after a 4300 kJ (1000 kcal) diet in which they lost an average 3.1 kg. This weight loss did not significantly alter melatonin levels.

Melatonin secretion has been proposed as a measure of noradrenergic neurotransmission in humans (Lewy, 1984; Checkley & Park, 1987). Initial studies suggested that melatonin levels were decreased in depressed patients (Beck-Friis *et al*, 1984; Claustrat *et al*, 1984; Brown *et al*, 1985) but in a recent carefully controlled investigation the trend was for depressed patients to have higher melatonin levels (Thompson *et al*, 1988).

Weight loss is a common feature in depression, especially of the melancholic or endogenous subtype, and it is therefore important to know whether weight loss itself may influence melatonin secretion. Positive (Arendt *et al*, 1982; Ferrier *et al*, 1982) and negative (Beck-Friis *et al*, 1984) correlations between weight and melatonin secretion have been reported. Two recent studies in anorexia nervosa have also produced conflicting results, with one study demonstrating an increase in mean 24-hour and overnight plasma melatonin levels compared with controls (Brambilla *et al*, 1988), and the other no difference in urinary excretion of the principal metabolite of melatonin, sulphatoxymelatonin (Bearn *et al*, 1988).

We studied the effect of moderate weight loss on melatonin secretion by measuring overnight plasma melatonin levels in normal volunteers before and after loss of about 3 kg in weight through dieting.

Method

Volunteers and diet

Ten female volunteers took part in the study, which was approved by the local ethics committee. They were selected to be of normal weight with a body mass index (BMI) (weight in kg / (height in m)^2) lying between 20 and 27 and to be without a personal or family psychiatric history or any history of endocrine abnormality.

The subjects undertook a 4300 kJ (1000 kcal) diet for three weeks as out-patients, and attended a research unit for testing before and at the end of the diet. The diet was begun a week after the woman's first tests so that the second set of tests might be performed at a similar stage of the menstrual cycle. One subject was taking a low-oestrogen contraceptive pill but the subjects were otherwise drug free.

The diet followed by the subjects was provided by the Department of Nutrition and Dietetics at the University of Oxford and has been described before (Goodwin *et al*, 1987). Essentially it provided 4300 kJ as 31% protein, 44% carbohydrate, and 25% fat. Subjects were weighed weekly and kept a diary of consumption to aid compliance. Weight loss was the main guarantee of compliance.

Melatonin measurement and analysis

This study formed part of a larger study examining the effect of weight loss on sleep-related hormone secretion (Anderson *et al*, 1989). Testing took place in a research unit on two pairs of nights with the first night of each pair serving as an adaptation night without blood sampling.

Hormonal sampling was performed via a specially adapted double-lumen intravenous cannula which allowed continuous blood sampling using a peristaltic pump. The blood was heparinised as it was withdrawn and passed through fine bore tubing to a fraction collector in an adjacent room. Blood samples were collected every 20 minutes, commencing between 22.00 and 23.00 h.

Plasma was separated by centrifugation (2000 r.p.m.) and stored at −20°C until assay. Mean plasma melatonin levels for each hour between 23.00 and 08.00 were obtained by pooling equal amounts of the three 20-minute plasma samples taken during that hour. Plasma melatonin was measured by a direct single-antibody radioimmunoassay (Fraser *et al*, 1983). The intra-assay coefficients of variation were 4.5% at 45 pg/ml and 6.6% at 115 pg/ml. The coefficients of variation between assays were 6.5% at 50 pg/ml and 8.1% at 110 pg/ml. The lower limit of sensitivity for the assay was 2.5 pg/ml. Samples from each individual before and after dieting were always analysed in the same assay.

Statistical analysis

Overnight plasma melatonin concentrations were analysed in two ways. First, individual values for each subject between 23.00 and 08.00 were summed over time to provide an index of overnight melatonin secretion on that occasion (total overnight melatonin) and the values obtained before and after weight loss were compared using a two-tailed paired t-test. Second, the data from each time point, which were normally distributed, were analysed using a two-way repeated-measures analysis of variance. Correlations were tested using Pearson's product–moment correlation. Group values are expressed as mean and standard deviation and mean difference with 95% confidence interval (95% c.i.) where appropriate.

Results

Details of the individual subjects are presented in Table I and the overnight secretion of melatonin illustrated in Fig. 1. All subjects tolerated the diet well, without clinically significant changes in mood, and all lost weight (mean 3.1 kg). Two subjects were tested at different stages of their menstrual cycle but their exclusion did not alter the results, which are therefore presented for the subjects as a whole. Total overnight melatonin before and after weight loss did not differ significantly ($t = 1.8411$, d.f. $= 9$, $P = 0.10$). Analysis of variance showed that mean plasma melatonin concentration changed significantly with time during the night ($F = 14.41$, d.f. $= 8{,}72$, $P = 0.0001$) with no overall difference between the two occasions ($F = 3.39$, d.f. $= 1{,}9$, $P = 0.10$). There was also no difference at any specific time point (time × occasion: $F = 1.62$, d.f. $= 8{,}72$, $P = 0.13$).

Total overnight melatonin did not correlate significantly with weight, BMI, or age (all $P > 0.1$), although the youngest subject had the highest, and the oldest subject the lowest values. The change in total overnight melatonin did not correlate with weight loss ($P > 0.1$).

Discussion

Our study suggests that moderate weight loss through dieting does not alter overnight plasma melatonin concentrations in female volunteers. A possible criticism of our study is that we measured melatonin secretion for only nine out of the 24 hours and may have missed any effects of weight loss in the early evening or late morning. However, for each subject we were able to detect an increase, peak, and decline in melatonin, and the similar shape of the melatonin curves before and at the end of the diet makes any 'phase shift' unlikely.

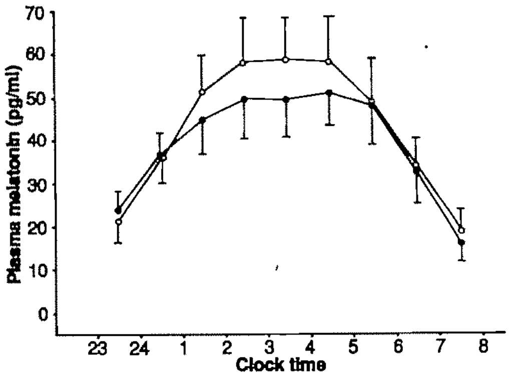

FIG. 1 Hourly overnight plasma melatonin concentrations for 10 women before (●——●) and at the end (○——○) of a three week diet (bars represent standard errors of the means).

The small number of subjects in our study mean that we could have missed an effect of weight loss, but the 95% confidence interval for the difference between individuals' total overnight melatonin on the two occasions (−8 to 76 pgh/ml) shows that at this level of significance we are only likely to have missed a 2% decrease in overnight melatonin concentration as opposed to a 22% increase. In the context of studies of melatonin secretion in depression our results make it very unlikely that a decrease in

TABLE I

Subject details, weight loss and total overnight melatonin secretion in ten women before and after dieting

Subject	Age: years	Pre-diet Weight: kg	Pre-diet BMI: kg/m²	Weight loss: kg	Melatonin: pgh/ml before weight loss	Melatonin: pgh/ml after weight loss	Melatonin: pgh/ml difference
1	22	67.3	23.3	3.2	538	598	60
2	24	66.5	23.0	1.9	381	382	1
3	27	62.7	22.3	2.0	323	336	13
4	24	59.0	23.3	4.1	184	274	90
5	30	51.0	21.2	3.3	225	202	−23
6	20	59.8	24.6	3.3	635	705	70
7	34	63.0	24.2	3.0	502	479	−23
8	38	58.8	24.8	4.0	93	88	−5
9	22	54.6	22.1	3.5	437	594	157
10	25	47.8	21.6	3.0	188	189	1
Mean	26.6	59.1	23.0	3.1	351	385	34
s.d.	5.8	6.4	1.2	0.7	178	204	
95% c.i.							−8 to 76

overnight plasma melatonin levels can be accounted for by moderate weight loss. However, our findings do not help to resolve the controversy about possible changes in melatonin secretion in patients with anorexia nervosa.

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Point of View

Vitamin Deficiency and Mental Symptoms

M. W. P. CARNEY

Recently, research into the connection between vitamins and psychiatric disorder, particularly affective changes, has been in the doldrums, with the exceptions perhaps of studies of folic acid and pyridoxine. The best way for research to proceed is first to establish that the association of a vitamin deficiency with a psychiatric disorder is beyond a chance finding. Then, questions should be asked about what mental symptoms it is linked with, and what the other associations (malnutrition, drugs, physical illness, etc) are. Lastly, queries should be raised about whether the association is causal or if the mental symptoms are merely secondary to the anorexia and poor diet so common in mental illness (or whether they are linked in a vicious circle as suggested by Reynolds *et al* (1971)). These questions became pertinent in the mid-1960s when reliable ways of assaying B vitamins such as folic acid became more generally available. In this review, I present evidence that deficiencies of folic acid, B12, thiamine, riboflavin, pyridoxine and ascorbic acid are not infrequently found in psychiatric practice. It should be remembered, however, that some ways of assaying vitamins are liable to give a larger proportion of spurious low results than other methods (false positives), although the adoption of more reliable ways of assaying vitamins should reduce this.

Thiamine deficiency

The severe classic syndromes of vitamin B deficiency like Wernicke's encephalopathy are rare in western clinical practice (e.g. Carney, 1971; Riding, 1975). However, milder biochemical deficiency in alcohol-related disease has been reported by Barnes (1978) and McLaren (1980). Irritability, aggressive behaviour and personality change were reported in human volunteers undergoing thiamine restriction (Word *et al*, 1980) and in adolescents subsisting on 'junk food' deficient in B1 (Londsdale & Shamburger, 1980). Fifty-eight of 154 psychiatric admissions with a history of poor diet had biochemical deficiency of thiamine (Carney *et al*, 1979). In most patients, the deficiency was the result of poor diet, and the spectrum of diagnosis was wide with no one condition predominating. In a later study (Carney *et al*, 1982), of 172 unselected patients admitted successively to the psychiatric unit of a district general hospital, 53% were deficient in one or more vitamin (41% in one, 12% in more than one), 30% of them in thiamine. There were significant excesses of schizophrenia and alcoholism among the patients with low-thiamine and multiple-vitamin deficiency. Furthermore, it was concluded that thiamine deficiency was usually secondary to anorexia rather than a causal factor. A high incidence of thiamine deficiency, mainly due to alcohol abuse, has also been described in Australian general hospital in-patients (Wood *et al*, 1986; Price *et al*, 1987).

Riboflavin (vitamin B2) deficiency

Little is known of the role of lack of riboflavin in the genesis of mental illness. Deficiency-related problems can be caused by hypothyroidism, adrenocorticotrophic hormone and aldosterone deficiency, phenothiazines, boric acid, oral contraceptives and alcohol, which all inhibit riboflavin's contribution to its co-enzyme derivatives that are biologically active (Rivkin, 1979). However, it is difficult to disentangle any unwanted psychiatric effects of these substances from the signs of riboflavin deficiency precipitated by them.

In one study of 210 New York adolescents of low economic status, and mixed Hispanic-American, black and white origins, Lopez *et al* (1980) found a 17% incidence of riboflavin deficiency or 23.3% using a different method of assay (26.6% after excluding those taking multi-vitamin preparations). None had relevant acute or chronic medical conditions or were pregnant, and only four were on oral contraceptives. Riboflavin deficiency has also been recorded among alcoholics. In a series of 35, abnormal values of red-cell glutathione reductase were found in 23% (Barnes, 1978). In another study of 13 alcoholics, two were found to be riboflavin-deficient (Bayoumi & Rosalki, 1976). Bonjour (1980*b*), however, thought that vitamin B2 deficiency in alcoholism was due to dietary deficiency rather than a direct toxic effect of the alcohol.

Carney *et al* (1982) found that 29% of 172 newly admitted patients to a general psychiatric ward were riboflavin-deficient. Although these patients did not show more clinical signs of deficiency or weight loss than non-deficient patients, riboflavin (and pyridoxine) deficiencies were associated with affective illness, endogenous depression and neurotic depression, while thiamine deficient patients had a variety of conditions in which under-nutrition seemed to be a common factor. There was no evidence that consumption of a particular drug or alcohol was responsible for the B2 deficiency. Riboflavin deficiency has also been linked with depression by Nobbs (1974).

Pyridoxine (vitamin B6) deficiency

Bonjour (1980*a*) felt that the pyridoxine deficiency in chronic alcoholism was due to liver damage. However, Lumeng & Li (1974) found 35 of 66 alcoholics with normal liver function to be pyridoxine deficient, and in a study by Carney *et al* (1979) none of the patients with low pyridoxine showed abnormal liver function. Moreover, Barnes (1978), found no evidence of pyridoxine deficiency in his group of alcoholics. The difference between Bonjour's results and those of these other studies may lie in the methods of estimation and also in the definition of alcoholism.

In a study of 64 psychiatric in-patients selected for a history of inadequate diet before admission, Carney *et al* (1979) found that 28 (44%) were deficient in B6 and 19 of these had an affective illness. Moreover, a lack of B6 was found in 15 (79%) of 19 endogenous depressives and only 13 (29%) of the 45 other patients. This link between pyridoxine deficiency and affective illness was subsequently reaffirmed (Carney *et al*, 1982). Indeed, of 238 patients assessed for riboflavin and/or pyridoxine status in two studies (Carney *et al*, 1979, 1982), 31 of 70 deficient patients were endogenously depressed compared with only 30 of 168 vitamin-deficient patients – a highly significant association between deficiency and endogenous depression ($P<0.001$). Although a comprehensive investigation of 12 vitamins, including pyridoxine, in Alzheimer's disease, multi-infarct dementia, depression and normal control patients found no differences in vitamin levels among these groups (Scileppi *et al*, 1984), a study of pyridoxine concentrations in psychiatric out-patients showed that 21% had low B6 and that this was linked with neurological-like symptoms in 19% (Stewart *et al* 1984).

Livingstone *et al* (1978) found no evidence of vitamin B6 deficiency in pre- and post-partum depressed women whose depression scores and mean pyridoxine concentrations were the same before and after birth. However, Holsboen *et al* (1985) found a reduction in scores of the Hamilton Rating Scale for Depression (Hamilton, 1960) in post- and pre-menopausal depressed women who were given oestradiol and pyridoxine, the reduction being greater in the former. Moreover, Adams *et al* (1973), in a double-blind trial, showed that pyridoxine was superior to placebo in alleviating depression in women with pyridoxine deficiency due to oral contraceptives. Finally, Hallert *et al* (1984) reported improvement in depression scores in B6-deficient patients with coeliac disease following B6 supplementation, whereas no improvement followed twelve months' gluten-free diet.

Cyanocobalamin (vitamin B12) deficiency

Table I shows the results of several surveys of serum B12 in psychiatric in-patients. The incidence of low B12 varies from 5.8 to 26.1%. Organic psychosyndromes were common in patients but many

TABLE I

Surveys of serum B12 in psychiatric in-patients showing percentages with low levels, and problems/disorders associated with this (definition of low varies according to the survey)

Authors and date of survey	*Total number in survey:* n	*Patients with low B12:* %	*Associated problems/disorders*
Carney (1967)	374	14.2[2]	Organic psychosyndromes/barbiturates, MAOIs & tricyclics.
Carney & Sheffield (1970)			
Carney & Sheffield (1978)	272	26.1[2]	Poor diet, alcoholism, organic psychosyndromes/ phenothiazines, benzodiazepines, tricyclics, MAOIs, barbiturates.
Carney *et al* (1989)	285	6[2]	—
Edeh *et al* (1983)	396	5.8[1]	1 case of pernicious anaemia.
Hallstrom (1969)	90	6.7[3]	About half had organic psychosyndromes.

1. Low < 100 pg/ml
2. Low < 150 pg/ml
3. Low < 170 pg/ml

of these had also abused alcohol. Diet was also shown to be poor in some cases. Medically prescribed drugs of various kinds (phenothiazines, benzodiazepines, tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) as well as barbiturates) were also found to be linked with low B12.

In an investigation of neurological and psychiatric sequelae in 84 patients selected on the basis of megaloblastic bone-marrow changes, Shorvon *et al* (1980) found that of 50 patients with B12 deficiency, 26% showed organic mental change, 16% subacute combined degeneration of the spinal cord, 40% evidence of peripheral neuropathy and 20% affective disorders. This diagnostic pattern was very much at variance with that of low-folate patients discussed in the next section.

Folic acid deficiency

Folate deficiency linked with dementia has been described in mentally disturbed geriatric patients (Sneath *et al*, 1973; Shulman, 1967*b*; Strachan & Henderson, 1967). Reynolds *et al* (1972) reported that folate-deficient medical patients had a significant excess of organic brain syndromes compared with normal folate patients.

Studies of *serum* folate in psychiatric patients have emphasised their liability to deficiency, especially in the case of depressed patients (10–30%). Table II includes the results of some of these studies. Carney (1967), for example, estimating serum folate in 423 consecutive psychiatric in-patients, found 105 (25%) with values below 2 ng/ml compared with only 6 (10%) of 62 normal controls (2 ng/ml was therefore taken as the cut-off point between normal and low serum values). Coppen & Abou-Saleh (1982), in a study of out-patients attending a lithium clinic, found an inverse relationship between plasma folate and affective morbidity. Serum folate, however, may be influenced by adventitious factors such as drugs and physical illness (Carney & Sheffield, 1970).

Red-cell (RBC) folate is a more valid index of tissue folate (Chanarin, 1982) but has only recently become available, although Reynolds *et al* (1971) used it to investigate mentally disturbed epileptics. A recent study of 285 general hospital psychiatric patients (Carney *et al*, 1990) showed that 34% had RBC folate values of less than 200 ng/ml and 12% had low values of less than 150 ng/ml (see Table II). Forty-three per cent of the depressed patients and 40% of the alcoholics had values below 200 ng/ml compared with 22% of manic, 17% of schizophrenic and 17% of normal mood state patients. Folate deficiency was most frequently found in endogenous depression. Other evidence that depression rather than anxiety is more frequently linked with folate deficiency derives from a community-based study by Edeh & Toone (1983).

In a survey by Gray & Leong (1986), however, only one patient had subnormal serum folate and the authors found no significant difference in folate level between depressed and non-depressed patients. Stern *et al* (1988), measuring serum and red cell folate in 17 out-patients taking lithium for prophylaxis of affective disorders, also found no correlation between folate levels and affective morbidity or lithium status. These two studies employed radically different methods of assay from the studies previously mentioned which may explain their different results.

Studies in folate replacement therapy indicate that folate deficiency is a causal factor in various

TABLE II

Surveys of serum and red cell (RBC) folate in psychiatric in-patients showing percentages with low levels, and problems/disorders associated with this

Authors and date of survey	*Number (n)*	*Proportion with low serum and/or RBC folate (%)*	*Associations*
Carney (1967)	423	25 (serum)	Endogenous depression, organic psychosis, chronic illness, physical illness, drug therapy, malnutrition.
Carney & Sheffield (1970)	75	50 (serum)	Alcohol, barbiturates, anticonvulsants.
Carney & Sheffield (1978)	272	21 (serum)	Depression, malnutrition, physical illness, anorexia.
Carney *et al* (1990)	285	12 (RBC folate)	In-patient status, endogenous depression, alcoholism.
Hallstrom (1969)	90	10 (serum)	Alcohol, barbiturates, anorexia.
Kalstrom & Nylof (1969)	115	20.9 (serum)	
Reynolds *et al* (1970)	100	24 (serum)	High depression scores, poor response to antidepressant drugs.

1. <2 ng/ml = low serum folate.
2. <150 ng/ml = low RBC folate (<200 ng/ml = low normal RBC folate).

disorders. A retrospective survey of two groups of folate-deficient patients (Carney & Sheffield, 1970), similar in terms of age and sex, found that 39 who had been treated with folate and B12 supplements were in a better clinical state at discharge and had had a shorter stay in hospital than the 63 untreated ones. Shorvon *et al* (1980), in a comparison of folate and B12 replacement, found that eight of nine folate-deficient patients who had complied with vitamin supplementation and follow-up for six months had made an excellent recovery compared with only eight of 16 vitamin B12 deficient patients. Botez *et al* (1984), having found mild organic brain damage (Wechsler verbal, performance, and full scales) as well as depression and minor neurological signs in folate-deficient patients, reported improvement following supplementation with folic acid. Furthermore, in a double-blind placebo-controlled trial of methyl folate in 37 folate-deficient depressives and schizophrenics, the folate-supplemented patients showed a much greater clinical and social improvement at three and six months. This held for the whole group and for the endogenous depressive and schizophrenic subcategories which were considered separately (Godfrey *et al*, 1988).

In addition to folate replacement therapy, there is other evidence indicative of the causal role of folate deficiency in some disorders. Deficiency is primary in some rare inborn errors of folate metabolism which may give rise to neuropsychiatric symptoms (Baumgartner *et al*, 1985; Smith *et al* 1986). Also, examples occur of antifolate drugs (e.g. methotrexate, trimethoprim and triamterene) which interfere with the enzyme dihydrofolate reductase (Lambie & Johnson, 1985) and thus have been reported to the Committee of Safety of Medicines on the basis that they cause depression. With other antifolate substances such as anticonvulsants, antituberculous drugs, alcohol and oral contraceptives, depression may also occur (Lambie & Johnson, 1985).

Ascorbic acid (vitamin C) deficiency

In animals, drug metabolism delayed by vitamin C and antipyrine half-lives were significantly longer in patients with liver disease who had the lowest levels of leucocyte ascorbic acid concentrations (Beattie & Sherlock, 1976). Specific mental changes with vitamin C deficiency include lassitude and depression (Walker, 1968). In experimentally-induced scurvy, Kinsman & Hood (1971) described personality change. Springer (1979) also described vitamin C deficiency in retarded children.

Fat soluble vitamin deficiency

Does lack of fat-soluble vitamins ever give rise to mental disturbance? There are anecdotal accounts of 'piblotko' or manic excitement linked with vitamin D deficiency among Eskimos (Carney, 1984). Keddie (1987) also reported a patient with hypercalcaemia and major depression in the context of hypervitaminosis D. This patient developed severe depressive illness after receiving inappropriate therapy with calcium gluconate and strong calciferol for 15 years. Unfortunately she apparently drowned herself after full correction of the metabolic disorder.

Conclusion

Although the classic syndromes of vitamin deficiency like beri-beri are now rare in the UK and the USA, subclinical deficiency is not uncommon – particularly thiamine, riboflavin, pyridoxine, folic acid and B12. Such deficiency is frequently found in endogenous depression and alcoholism. While depression seems to be characteristic of most vitamin B deficiencies, in B12 deficiency, organic psychosis is the typical psychosyndrome with affective symptoms taking second place. Thiamine deficiency is linked with a wide variety of mental symptoms and is probably secondary to anorexia and malnutrition. Ascorbic acid deficiency seems to be linked with depression and apathy. It is likely that the deficiencies in folic acid and vitamin B12 have a primary role in some disorders but the causal role of the lack of other vitamins is unclear.

Systematic long-term follow-up studies and large placebo-controlled trials of replacement therapy with respect to the B and C vitamins have rarely been done. There are good practical and theoretical reasons for remedying this.

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A Variant of Capgras Syndrome with Substitution of Inanimate Objects

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An unusual and rare variant of Capgras syndrome is reported in which a patient with depressive illness became preoccupied with doubles of inanimate objects. The patient responded to antidepressant therapy.

Capgras syndrome is a rare disorder characterised by the patient's delusional belief that another person, usually someone closely related, has been replaced by an exact double. It was first described by Capgras & Reboul-Lachaux (1923), who referred to it as *l'illusion des sosies*; *'sosie'* originating from Plautus' play *Amphityron* in which the god Mercury became the double of Sosie, the servant of Amphityron (Enoch & Trethowan, 1979). It occurs in a setting of clear consciousness and is usually accompanied by other paranoid phenomena of schizophrenic or affective nature although it has also been described in organic states.

As a particularly rare variant, the patient may believe that some inanimate object has been replaced by an exact replica. In some cases, the identical-looking objects have been replaced by the relative's double and this is therefore an extension of the classic form of the Capgras syndrome (Bouvier, 1926; Brochado, 1936). Thus, Coleman (1933) reported the case of a woman with 'involutional melancholia' who believed that her daughter's letters had been replaced by facsimiles written by someone else, and also cited a report by Courbon (1932) in which a woman with melancholic depression believed that her "new coat had been replaced by a dilapidated and shabby one". Enoch & Trethowan (1979) described a case of a 22-year-old university student suffering from acute schizophrenia, who believed that her watch had been replaced by a clever copy made by the police and so threw it into a stream. Such cases have been regarded as fragmentary variants of Capgras syndrome.

This paper documents a case of Capgras syndrome in which the patient reported that her spectacles had been substituted by an identical pair.

Case report

A 57-year-old caucasion woman was first seen by psychiatric services in 1977 for a depressive illness following her husband's death by drowning. She was low spirited, had impaired concentration, was unable to cope with her day-to-day activities and showed signs of self-neglect. She responded to supportive psychotherapy as a day patient. Following her recovery she had bouts of depression which were treated by her general practitioner with dothiepen. In April 1979 she was referred again to the psychiatric services because of worsening symptoms; she was treated with supportive psychotherapy as an out-patient, and by August 1979 had recovered.

In early 1981, when seen on a domiciliary visit, she was suspicious in manner, but her only complaint was that someone had stolen her spectacles and replaced them with an identical pair that did not belong to her. Although these fitted well and she could see with them she refused to wear them. She said that without her own spectacles she could not carry out her chores in her flat or go shopping; there were, however, no signs of neglect within her home and she paid regular visits to the shops opposite to purchase essential goods. She denied any depressive symptoms and showed no clinical features of schizophrenia, mania or organic cerebral impairment. She lacked insight and refused treatment.

Further home visits were undertaken to assess her in greater detail and to gain her trust. By September 1981 she had agreed to a trial of treatment with fluphenazine decanoate (25 mg) given intramuscularly every four weeks. Between January and June 1982 she developed a clinical picture of depressive psychosis. In July 1982, she was admitted to the psychiatric ward where she denied any florid delusions but remembered about the spectacles being replaced without any concern or worry. On this admission fluphenazine decanoate was withdrawn and she responded to dothiepen. Her improvement was maintained until September 1982 when she was discharged from the hospital.

Discussion

Most case reports of Capgras syndrome have shown associated psychiatric symptoms or organic condition. MacCallum (1973) reported a case of a 44-year-old woman with the diagnosis of endogenous depression who became convinced that she and the hospital staff were exact replicas of what she had known them to be. Delay *et al* (1952) described a case where the patient was convinced that she had been transferred from one room to another while she was asleep, the second room being a replica of the first. Another report (Christodoulon, 1977) described a case of a 43-year-old married housewife with the diagnosis of paranoid schizophrenia, who believed that her husband had died and an identical-looking man had taken his place. She also reported that her husband's double took away her belongings and replaced them with identical objects.

These reports suggest that occasionally patients with Capgras syndrome become preoccupied with doubles of inanimate objects connected to them intimately. The intimacy suggests either a symbolic attachment to or the significance of the inanimate object in question; alternatively, the object may have become an extension of self. In this case it is reasonable to assume that the patient may have had a subsconscious desire, probably based on depressive cognitions, to avoid the world, which was "not a beautiful place to see".

This case has many similarities with that reported by Coleman (1933). Both patients had a clinical picture of severe depressive illness with no clear signs of schizophrenic or organic psychosis. In addition, the patient's history showed strong evidence of recurrent affective states. It is not surprising, therefore, that neuroleptic treatment had no effect while there was rapid and complete response to antidepressant therapy.

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Seasonal Affective Disorder Following Brain Injury

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Seasonal affective disorder has not previously been linked with neuroanatomical abnormalities despite its relationship to biological rhythms. A 45-year-old woman is described with an arteriovenous abnormality in the right frontotemporal region who developed recurrent winter depression and summer hypomania.

Seasonal affective disorder (SAD), a condition first described by Rosenthal *et al* (1984), is characterised by seasonal patterns of depression. In most cases the depressive syndrome develops during the autumn or winter, remitting by the following spring or summer but recently a variant with summer depression has been described (Wehr *et al*, 1987). During their depressive episodes, patients frequently experience an increased desire to sleep and an increased appetite for sweet foods, both of which fall into the category of atypical depressive symptoms. SAD has been recognised and described in England (Thompson & Isaacs, 1988), Switzerland (Wirz-Justice *et al*, 1986) and Australia (Boyce & Parker, 1988) as well as in various parts of the United States. In most series a majority of patients fall into the diagnostic category of bipolar-II disorder according to the Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978).

In none of the reported series has any mention been made of head injury or other cerebral pathology. Yet affective disorders are frequently seen in association with cerebral damage; in these patients, depression appears to be more commonly associated with lesions in the left hemisphere (Robinson *et al*, 1984), and mania with lesions in the right hemisphere. In one series of 17 brain-injured patients presenting with mania (seven of whom had a bipolar course), mania was associated with right hemisphere lesions in 12, mainly involving areas related to the limbic system; of the remainder, all but one had bilateral lesions (Robinson *et al*, 1988).

The question then arises, can a lesion in the right limbic area give rise to SAD, a variant of bipolar disorder? We report a patient with recurrent winter depression and summer hypomania who fulfils the criteria for SAD and in whom there is a clear-cut intracerebral pathology involving the right limbic area.

Case report

Ms B, a 45-year-old married woman, has a 13-year history of recurrent depressive episodes which in recent years have shown a seasonal pattern. At the age of 17 years she presented with a sudden-onset left-sided hemiplegia. Cerebral angiography revealed an arteriovenous abnormality in the deep white matter of the right cerebral hemisphere. This was treated with radiotherapy and she was left with a mild left-sided hemiplegia, partial hemianaesthesia, and complete homonymous hemianopia.

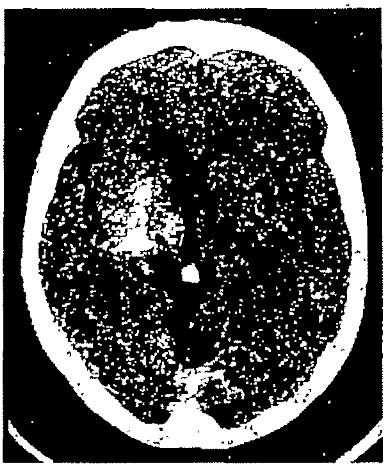

FIG. 1. A computerised tomography scan (1988) of the woman, showing a contrast-enhancing lesion in the right hemisphere in the deep white matter of the frontal and temporal region.

Although she had been advised not to become pregnant, she did so at the age of 31. She gave birth to a healthy girl but soon after her Caesarian section she had a further minor cerebral bleed which was treated conservatively and her disability was little changed and has subsequently remained static. A computerised tomography (CT) scan in 1988 showed a contrast-enhancing lesion in the right hemisphere in the deep white matter of the frontal and temporal lobes (Fig. 1).

Her first depressive episode began within two months of childbirth and persisted for ten months before treatment with amitriptyline. Her symptoms resolved over the following two months. During the next two years she suffered three further depressive episodes lasting for three to four months each. For a period of four years (1979–82) she received prophylactic treatment with lithium, during which time she remained well.

From the winter of 1982 onwards a marked seasonal variation in mood, energy, socialisation and sleep has developed. She becomes depressed in September with her mood lifting in March. During the winter of 1984–85 she took an overdose and jumped from a first-floor window, without serious sequelae. In the winter of 1985–86 she again became depressed. She had heard from a relative in the USA about light treatment and her husband imported bright lights from the USA and she started to use them. She abandoned this as she found using the lights 'too disturbing' when all she wanted to do was sleep. With each depression she experienced hypersomnia (12 hours, compared with six hours in the summer) but little change in appetite or weight. During each summer she was described by her general practitioner as exhibiting an 'exaggerated cheerfulness', she felt an increase in energy, became more active at work and in the home, took up new interests and felt so confident that her disabilities no longer deterred her from any activity. This is suggestive of mild manic episodes.

She was referred to one of us (TS) at this time and treatment with lithium carbonate was restarted. During the winter of 1986–87, while taking lithium (12 h level = 0.8 mmol/l) she did not become depressed at all for the first winter in five years. She stopped treatment in April 1987 and remained well until November 1987 when her depression returned and she was admitted. Her symptoms resolved over three weeks during admission and treatment with imipramine. Since then she has been treated with lithium and remained well throughout the summer of 1988 and winter of 1988–89.

There is no known family history of affective illness, nor of any other psychiatric disorder. Her father does not report a major personality change at the time of her first cerebrovascular accident. Throughout her adult life she has made and maintained relationships, taken good parental care of her daughter and worked consistently, when well, as a secretary and receptionist.

Discussion

This patient meets the criteria for SAD suggested by Rosenthal *et al* (1984) of (a) a history of major affective disorder, and (b) at least two consecutive winter depressions remitting by the following spring. However, she does not meet the exclusion criteria of another axis-I disorder or psychosocial variable that would account for the variability in mood. She experienced hypersomnia but not increased appetite, both of which are common but not essential features of SAD. As with many in the American (Rosenthal *et al*, 1984) and the Swiss series (Wirz-Justice *et al*, 1986) she can, in addition, be classified as suffering from a bipolar-II affective disorder according to RDC. It has been suggested (Thompson & Isaacs, 1988) that SAD may be a particularly 'biological' subtype of affective illness in which the annual rhythms are disturbed. Therefore this patient is of particular interest in that her SAD is associated with clear-cut structural brain damage. The site of the lesion in this patient is similar to that found in patients suffering from mania after brain injury (Robinson *et al*, 1988), and is consistent with the view that bipolar affective disorder (and its seasonal variant) may be associated with an abnormality in the deep temporofrontal region on the right side of the brain.

This case illustrates the association between major psychiatric disturbance and brain dysfunction. Further study of brain-injured groups may show a higher incidence of SAD than in the general population and may yield further information on the anatomical regions associated with SAD, thus helping to elucidate the inter-relationship between season, mood, and brain function.

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Manic–Depressive Psychosis in a Mentally Handicapped Person

Seasonality: A Clue to a Diagnostic Problem

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Diagnosis of mental illness in mentally-handicapped people is often difficult and complex, because of atypical presentation and lack of clear diagnostic criteria. A patient in whom seasonal variation in behaviour and mood gave a clue to the diagnosis of manic–depressive psychosis is reported.

Clinically it is important to make a distinction between manic–depressive psychosis and schizophrenic illness, yet the difficulties associated with such distinction are familiar to all clinicians. To quote Heaton-Ward (1977): "Mental illness which appears to be developing into a classical case of one particular psychosis may often prove to be an undoubted case of another when reviewed over a period." Difficulties in diagnosis of mental illness in mentally-handicapped people are even greater because of their unusual symptoms and difficulties in communication and expression.

Seasonal changes in the incidence of affective disorders are well documented (Symonds & Williams, 1976). Here, a case is reported of a mentally-handicapped woman with an original diagnosis of schizophrenia in whom seasonal changes of activity and behaviour led to the diagnosis of manic–depressive psychosis.

Case report

Miss C, a 22-year-old single woman, is the youngest in a family of four children, all of whom are of low intelligence. She is mildly mentally-handicapped (IQ = 62). She can communicate well, perform all basic tasks, and has self-help skills. She can copy words and read to a certain extent, but her ability to conceptualise numbers and figures is limited.

Her antenatal and natal history was uneventful. Very little information is available on early developmental history. Her mother is also a woman of limited intelligence and has been married twice, both marriages ending in divorce. All the children were born out of her first marriage. In the absence of a stable marriage, the mother experienced particular difficulties in coping with the two youngest children, which led to Miss C attending a residential special school away from home and the youngest son staying at a children's home. There is no suggestion of there being an organic cause to the mental handicap in any of the siblings or the mother and it seems likely that it is of sociocultural aetiology. There is no family or past history of any psychiatric disorder and Miss C denied abusing drugs or alcohol.

She was first referred to psychiatric services in October 1982. At that time she was attending the residential special school and was sent home because of her disturbed behaviour. On arrival at home her mother described how she was withdrawn and almost mute, and how her gait and eating were slow. She was aggressive towards her mother and peers at school. On admission she appeared vague, perplexed and deluded. Her affect was inappropriate and she was reported to have auditory hallucinations but was unable to expand on these. A diagnosis of schizophrenia was made and she was treated with haloperidol. She was discharged home after four weeks and returned to school in January 1983.

She became disturbed and aggressive again in March 1983, at school. She was overactive, overtalkative, had increased appetite and disturbed sleep. Often her behaviour was childish and silly, of a histrionic attention-seeking type. In April 1983, after leaving school, she started attending an adult training centre where her behavioural problems became worse. She also became sexually disinhibited towards men. There was no evidence of any delusions or hallucinations. As an in-patient from May 1983 she was treated with neuroleptics but, despite heavy doses of haloperidol (20 mg t.d.s.), she remained difficult to manage until the end of August 1983, when she started to settle gradually. She was discharged home in November 1983.

In April 1984 she started to become anxious, agitated, hyperactive, and aggressive. She was preoccupied with fears and gave inappropriate answers on interview. Her mood fluctuated from being happy and euphoric for a few days to feeling low for a few days and was also normal sometimes. She admitted to hearing voices but could not elaborate on them. A diagnosis of mixed affective/schizophreniform disorder was made and she was treated with oral and depot neuroleptics. Despite treatment she remained disruptive, attention seeking and aggressive until the end of August 1984.

On one occasion she arrived at the casualty department of a general hospital where she behaved in a histrionic manner and collapsed. In September 1984 she was prescribed lithium carbonate, the dose gradually being increased from 400 mg to 800 mg daily. She showed marked improvement within two to three weeks, with a return of normal behaviour and mood. Serum lithium levels were monitored every month (range: 0.6–1.1 mmol/l). In March 1985, her compliance to lithium became erratic while at home, and she stopped taking it. Within a few weeks she started to become excited, agitated and aggressive, and there was a grandiose element to her thinking. She had to be readmitted to the hospital. Lithium therapy was re-introduced in May 1985 and she has been on lithium carbonate (800 mg daily) since.

She has improved dramatically and presented with very few management problems over the past three years. Serum lithium levels are monitored every three months (usual range: 0.7–0.9 mmol/l). She has also been able to sustain a part-time job as a kitchen assistant in a local restaurant for the past eight months and it is envisaged that she will move into a hostel-type supervised accommodation run by the social services department.

Discussion

This case clearly reflects the difficulties encountered in reaching a definite diagnosis of mental illness in mentally-handicapped persons. She presented with a wide range of symptoms and signs, none of which led to a definite diagnosis at the time, although retrospectively they seemed to fit in with the diagnosis of manic–depressive illness. The difficulty of diagnosis was largely due to the changes in mood being ill-sustained, the childlike and fantasy thinking and the often silly, histrionic attention-seeking behaviour.

Reid (1972) has shown the importance of recognising manic–depressive psychosis in mentally-handicapped persons. Often the close study of symptoms and natural history of illness suggests the correct diagnosis.

Several authors have shown an association between the season and incidence of depression and suicide (Rosenthal *et al*, 1984; Zung & Green, 1973) and mania (Symonds & Williams, 1976). Seasonal affective disorder (SAD) is described as a subgroup of the affective disorders, a syndrome characterised by recurrent depression that occurs at the same time each year. Rosenthal *et al* (1984), in a report of 29 patients in whom depression was manifest in winter, suggested that the criteria for the diagnosis of SAD should be "at least two consecutive years in which the depression has developed during fall or winter and remitted by following spring or summer".

Most of the patients presenting with recurrent seasonal depression suffer from bipolar affective disorder. In the patient reported here, the initial episode in September 1982 may be seen retrospectively as a 'depressive phase'; otherwise, she consistently presented with manic phases during each subsequent summer. The patient spent most of the winter months over this period at home with her family but never presented with management problems. It is still possible that she had depressive phases during winter which went unnoticed by the family, a phenomenon which has been observed by Hasan & Mooney (1979).

The most outstanding feature of patients with seasonal affective disorder is their apparent sensitivity to change in season (and latitude), and thus the approximate annual occurrence of their affective episodes. Of the various possible climatic variables, day length or daily hours of sunshine seems to be the most promising candidate for future study, particularly following the discovery that bright light can be used to treat recurrent winter depression (Rosenthal *et al*, 1984).

Mawson & Smith (1981) found a negative correlation between relative humidity and episodes of mania. Seasonal changes in biochemical variables related to affective disorder have been widely investigated (Wirz-Justice & Richter, 1979; Swade & Coppen, 1980), particularly the serotonin system. The effect of light is highlighted by the evidence that patients with affective disorder have been shown to be hypersensitive to the suppressant effect of light on melatonin, the pineal hormone that mediates various light-dependent seasonal rhythms in animals.

We also looked at the various life events and changes in her environment to see if there was any relationship of these to the onset of manic episodes. Although in April 1983, the first episode of excited behaviour was closely related to her leaving school and joining the adult training centre, there was no evidence of any such link with a significant life event in subsequent years. There was, however, a connection with the seasons since disturbed behaviour occurred mainly during the summer months.

Efficacy of lithium in the management of manic–depressive psychosis is well established in longitudinal studies (Baastrup & Schou, 1967; Amdisen, 1970) and in controlled studies (Baastrup *et al*, 1970; Cundell *et al*, 1972). There has been a marked improvement in the mental health of the patient reported here since the introduction of lithium, which further stresses the need for early identification of manic–depressive illness in mentally-handicapped persons. Owing to inherent difficulties in such diagnosis, one has to resort to various clues. The authors suggest that long-term recording of patients' behaviour and general activity, with a view to identifying any seasonal variations, may often provide such clues.

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Calcium-Channel Blockade and Depressive Illness

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A case of depressive disorder in which treatment resistance was associated with the calcium-channel blocker nifedipine is described.

There has been much interest in the use of calcium-channel antagonists in psychiatric disorders. In particular, verapamil has been used in the treatment of mania (Dubovsky *et al*, 1982; Giannini *et al* 1984). Paradoxically, a case of mania reported by Zolese & Henryk-Gutt (1987) which was attributed to a low-energy diet and myxoedema was subsequently suggested to be the result of the administration of nifedipine, another calcium-channel blocker (Tacke, 1987). Hullett *et al* (1988) described four cases of depression associated with nifedipine prescription, including one where standard treatment was rendered ineffective.

We present a case of long-standing unipolar affective disorder in which treatment resistance disappeared on withdrawal of nifedipine and was followed by a period of elevated mood.

Case report

The patient was a 67-year-old woman who had a 40-year history of recurrent depression which fulfilled the DSM–III criteria (American Psychiatric Association, 1980) for major affective disorder and included hypochondriacal delusions. There was no evidence of bipolarity. Although her condition had previously responded to standard treatments, she was referred from another psychiatrist after a three-year episode of depression unresponsive to a wide spectrum of antidepressants and two courses of electroconvulsive therapy. She had commenced treatment with nifedipine for hypertension shortly after the onset of the current depressive episode and was also a diabetic controlled on diet alone.

Subsequently, she had a number of admissions to our unit specialising in the treatment of severe affective disorder. Drug combinations (Cowen, 1988) were used as well as carbamazepine, sodium valproate and fluoxetine. The patient failed to respond. She also received two courses of ECT totalling 20 clinically adequate convulsions but resulting in only partial and transient remission of symptoms. She seldom remained out of hospital for more than a few months and was never symptom-free.

Following a suicide attempt by hanging, and considering the distress suffered by the patient and her family, she was admitted for assessment for psychosurgery. On admission, the patient suddenly and inexplicably recovered.

A study of the prescription of drugs revealed the introduction of clomipramine (50 mg b.i.d) on day one. On day three nifedipine was reduced from 40 mg to 20 mg per day because of the development of hypotension. On day 16 nifedipine was reduced again to 10 mg per day and there was a further reduction on day 18 to 5 mg per day. The clinical improvement was very rapid. On day five she was described as 'quite cheerful' and on day eight as 'much brighter'. Within two weeks she was coping well at home and at interview was described as animated and symptom-free. Within two months she described herself as being 'wonderful': "I feel so well I can't wait for the next day to come." Indeed this state was quite unusual for her and although not hypomanic, the level of mood was probably above her normal. This state of well-being continued for seven months until she developed an arterial occlusion of her leg. Her condition deteriorated and she died of a pulmonary embolism. Following her death the family took the trouble to write to the unit expressing their thanks for how well their mother had been in the last few months of her life.

Discussion

A review of 45 consecutive patients referred to the unit with severe affective disorder over two years (but excluding our index case) revealed that eight were on medical treatment and, of these, four were on nifedipine. Three recovered on withdrawal of nifedipine but remained on various drug treatments for affective disorder. The final patient recovered on withdrawal of nifedipine alone.

The mild elevation of mood noted in our index case was seen in one other patient with chronic unipolar depressive disorder who stopped her own nifedipine treatment and described herself as 'marvellous', while her family noted she was 'overtalkative'. There was also a suggestion of a 'switch' process over a period of hours from depression to well-being.

It is of course possible in the index case that recovery occurred spontaneously or was an early result of the administration of clomipramine. However, this is not supported by the course of illness or the previous treatment failure with the highly specific 5-hydroxytryptamine (5-HT) re-uptake inhibitor fluoxetine. While there is an association between chronic depression and concurrent medical illness (Akiskal *et al*, 1981), the prescription rate of nifedipine in our series is equal to that for all other medical treatments, supporting our suggestion that there may be a causal link between the drug and resistant depression.

Given the hypothesis that depressive disorder is a result of deficient monoaminergic transmission, Hullett *et al* (1988) proposed that nifedipine's ability to antagonise the effects of noradrenaline may explain the association with depression. There are also reports of nifedipine being effective in Tourette's syndrome (Goldstein, 1984; Berg, 1985), blocking amphematine-induced behavioural stimulation in mice (Greb, 1986), and precipitating an oculogyric crisis in a neuroleptic-treated patient (Singh, 1987). This would all suggest a propensity to reduce the activity of monoamine systems. It is therefore paradoxical that nifedipine reduces immobility in the mouse behavioural despair test which has been proposed as an animal model for antidepressant action (Mogilnicka *et al*, 1987). However, even if the animal model is accepted, it is based upon the short-term effects of single doses which may not have the same effects upon monoamine systems as more chronic usage. For instance, Wolchinsky & Zsoter (1985) reported that calcium-channel blockers may temporarily increase noradrenergic activity, leading to a depletion of neurotransmitters.

Explanations based on the monoamine hypothesis could not easily account for nifedipine precipitating mania (Tacke, 1987) nor for its withdrawal causing abnormal elevation of mood in our two patients with unipolar affective disorder. There is increasing interest in the role of intraneuronal calcium in psychiatric disorder (e.g. Dinan, 1987) and consideration of its place in bipolar affective disorder is relevant to our case.

Calcium plays an important role in the regulation of cellular function. Rapid, pulsatile increases in its intracellular concentration act as signals for the initiation of biochemical events and may be part of the transduction process between receptor activation and effector mechanisms. Calcium may enter the intracellular pool through voltage-sensitive calcium channels in the cellular membrane which are triggered by depolarisation. Some of these channels are sensitive to blockade by dihydropyridines such as nifedipine (Campbell *et al*, 1988). Intraneuronal calcium concentration can also be increased via the inositol polyphosphate system. Activation of receptors, including those for noradrenaline and 5-HT, leads to the production of two second messengers, inositol 1,4,5-triphosphate and diacyl glycerol, which regulate release of sequestered calcium from intracellular organelles (Nahorski *et al*, 1986; Miller, 1988). Lithium at concentrations therapeutic in people is capable of inhibiting crucial steps in inositol polyphosphate metabolism, thereby altering the sensitivity of the neurone. This has been suggested as the basis of its therapeutic role in bipolar illness (Berridge *et al*, 1982). Modulation of voltage-sensitive calcium channels by dihydropyridines may also alter neuronal sensitivity (Dinan, 1987). Thus nifedipine could have a destabilising effect opposite to that of lithium which would explain its implication in both depressive illness and hypomania.

The calcium-channel antagonists are structurally and pharmacologically heterogeneous (Henry, 1980). Verapamil does not bind to the same receptor as nifedipine (Snyder & Reynolds, 1985) which explains the apparent paradox that the former may stabilise mood while the latter may precipitate affective disorders. Certainly, our data suggest that patients with treatment-resistant depression who are receiving nifedipine should have this drug changed to one which does not interfere with calcium influx. For the future, the possibility of the therapeutic use of calcium-channel agonists in affective disorder should also be considered.

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A Fatal Case of Water Intoxication in a Schizophrenic Patient

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A fatal case of water intoxication in a schizophrenic female Chinese patient is described, including post-mortem findings.

This paper highlights the subject of mortality associated with water intoxication among psychiatric patients, and reports a fatal case from Singapore.

The lack of documented reports suggests that mortality due to water intoxication is rare. If the serum sodium level falls below 125 mmol/l in less than 24 hours, the mortality rate and risk of brain damage increases (Arieff & Guisado, 1976). The earliest case of fatality was reported by Helwig *et al* (1935). Other cases have been reported by Raskind (1974), Rendell *et al* (1978) and Di Maio & Di Maio (1980).

Case report

The subject was a 40-year-old married Chinese woman, whose first schizophrenic breakdown (ICD-9 criteria; World Health Organization, 1978) occurred in 1972 at the age of 28. She presented with auditory hallucinations in the second person and persecutory delusions directed against her family, but showed no disturbance in her mood or cognitive state. She was the sixth in a family of seven siblings, and her younger brother had also suffered from psychosis. Between 1972 and 1984 she had a total of 13 admissions for relapse: most of these were during 1982–84. During relapses she had delusions, hallucinations and volitional disturbances. There was no evidence of a mood disorder throughout her illness. She attended clinic regularly for treatment (although she defaulted for a period in 1981): fluphenazine decanoate was injected (usually 25 mg monthly); also chlorpromazine was taken orally (50–300 mg a day). Trifluoperazine (10–15 mg a day) was added between March 1983 and April 1983. (Between 1975 and 1977 she had been prescribed lithium carbonate because of aggression during relapses but this had been stopped after she developed tremors of the arms.)

She was also found to have diabetes mellitus in 1982 and was put on oral hypoglycaemics, initially chlorpropamide and later tolbutamide (500 mg t.d.s.), which resulted in good control of blood sugar levels. She had no history of hypertension.

In March 1984 she was admitted after she had quarrelled with her husband. For three months before that she was paranoid about her husband and a woman neighbour, during which time she received intravenous fluphenazine decanoate (25 mg monthly) as well as oral chlorpromazine (100 mg t.d.s.), benzhexol (2 mg t.d.s.), trifluoperazine (5 mg t.d.s.) and tolbutamide (500 mg t.d.s.). The ward nurses noticed that she had polydipsia. She became confused, threw a generalised fit, became comatosed and was transferred to a general hospital after an intravenous dextrose–saline drip was set up. She arrived in a coma. After admission to the medical ward, her sodium level was found to be low (124 mmol/l, normal 135–145 mm/l) but her potassium level was normal (3.9 mmol/l). Her plasma osmolality was also low (243 mmol/l, normal 275–305 mmol/l) as was her urine osmolality (285 mmol/l, normal 500–1200 mmol/l). A computerised tomography scan (CT) of her brain, lumbar puncture findings, and a chest X-ray were normal. Blood sugar level was 255 mg/dl. An electrocardiogram (ECG) showed regular sinus rhythm pattern, and augmented volt foot, suggestive of ischaemic heart disease and an old inferior myocardial infarct. A previous ECG in 1980 had been normal. She recovered with fluid restriction, and her sodium level returned to 135 mmol/l while her two-hour post-prandial blood sugar level fell to 187 mg/dl and, two months later, to 120 mg/dl. However, no urea/electrolyte levels were determined after discharge from the medical ward. Her mental state stabilised and she was not confused.

Five months later she relapsed and was again admitted, presenting with paranoid delusions about her husband. She was given intravenous fluphenazine decanoate (37.5 mg) on admission and was given oral chlorpromazine (100 mg *nocte*), benzhexol (2 mg b.d.) and tolbutamide (500 mg t.d.s.). During the one week of admission, she was noted to be drinking tap water excessively (but the quantity or frequency was not recorded), and was sometimes confused.

On 23 August 1984, she threw a fit, fell and hit her head. There was only loss of consciousness for about one minute. She was transferred to a general hospital after being given 40 ml of intravenous dextrose (50%) and a dextrose (5%) drip was set up, running at a slow rate. About 250 ml of intravenous fluids were given. (Hypoglycaemia was suspected by the duty medical officer who was not aware of her history of water intoxication.) On arrival she was restless and confused, cyanosed, sweating, and frothing at the mouth. Her blood pressure was 190/110 mmHg and her lungs had bilateral rhonchi and crepitations. After arrival her plasma levels were urea 6 mg/dl, sodium 109 mmol/l, potassium 3.3 mmol/l, chloride 80 mmol/l and glucose 408 mg/dl. Blood gases showed poor oxygenation but ECG and cardiac enzymes were not indicative of an acute myocardial infarct.

In the medical ward she was managed for acute pulmonary oedema but had cardiac arrest one hour later and died.

A post mortem carried out showed that lungs were severely congested and oedematous. The brain showed cerebral oedema with prominent tonsillar herniation. There was no fracture but a bruise (2.5 cm diameter) was noted on the left occipital scalp. There was no intracranial haematoma or haemorrhage. The cardiovascular system showed evidence of ischaemic heart disease, with 80% occlusion of the left anterior descending branch of the coronary arteries and 50% occlusion of the left circumflex branch. However, the epicardium and myocardium were found to be healthy. The kidneys and the liver also showed congestion.

Discussion

The diagnosis of water intoxication in this case is based on clinical findings of polydipsia, confusion and convulsions, as well as on biochemical findings of hyponatraemia, and low serum and urine osmolality. Our findings of hyponatraemia are consistent with other case reports on water intoxication (Harisprasad *et al*,1980) while Rendell *et al*'s (1978) case had features of pulmonary oedema similar to ours. In addition, the post-mortem findings of transtentorial herniation and cerebral oedema were also seen in the cases of Helwig *et al* (1935) and Raskind (1974) while animal experiments have demonstrated that water intoxication can lead to cerebral oedema (Helwig *et al*, 1935; Wasterlain & Posner, 1968).

However, this case is complicated by the patient's additional diagnosis of diabetes mellitus. With regard to the high blood sugar level, this was most likely to have been caused by the intravenous glucose that was administered. Although it was possible that this led to a spurious hyponatraemia, this could not explain the post-mortem finding of cerebral oedema as well as the extremely low sodium level. Taking the first instance of fits in this patient, if the hyponatraemia was a result of the hyperglycaemia, then the plasma osmolality level measured would have been normal, not low. In the second instance of fits, unfortunately the plasma osmolality was not measured in the rush of the medical emergency, but the osmolality calculated for the plasma glucose and sodium is low, suggesting water intoxication as the true problem rather than a complicated diabetes mellitus.

As to the cause of death, it could hardly have been due to overtransfusion as the intravenous drip was running at a slow rate. Head injury can also be ruled out as a cause of death, as post-mortem examination did not show any intracranial bleeding and there was only transient loss of consciousness at the time of fit.

The cause of death in this patient was actually recorded as ischaemic heart disease. This is technically correct because of the degree of blockage of the coronary vessels. However, since myocardium was healthy, this does not give a true picture of her death, which we believe is due to cardiac arrest caused by fluid overloading, with pulmonary oedema and electrolyte imbalances, when her heart had already been compromised by ischaemia. In addition, the cerebral oedema was a contributory cause to the death, causing tonsillar herniation of the brain. Death in water-intoxicated patients is usually attributed to pulmonary or cerebral oedema, as in the cases of Rendell *et al* (1978) and Raskind (1974).

Vieweg *et al* (1985), found that as many as 18% of the deaths of schizophrenic patients under 53 years-old may be related to water intoxication. If the psychiatrist is alert to its possibility, then early diagnosis and prevention of water intoxication may help reduce fatalities.

What are some of the practical lessons that may be learnt from the management of this case?

Identification and evaluation

There was no history of excessive water drinking at home although this could have been mistaken by the family or patient as 'normal', or could have been hidden by the patient. Unexplained first episodes of fits in psychiatric patients should lead the clinician to have a strong suspicion of water intoxication, as in this case. The presence of hyponatraemia is an essential confirmation of the diagnosis.

The quantity and frequency of the fluids consumed and the urine output was inadequately reported in the ward. To give a detailed report, however, can prove difficult unless it is a ward with a high staff : patient ratio. The use of medications and their time relation to the episodes of water intoxication should be noted. Even after the acute management, the electrolyte and osmolality levels, and the urine specific gravity should be checked at regular intervals. Weighing of the patient at regular intervals in the day is a useful indication of fluid retention and can help in the diagnosis (Delva & Crammer, 1988).

Management

If the laboratory investigations point to a possible syndrome of inappropriate antidiuretic hormone secretion (SIADH), based on an inappropriately concentrated urine with a hypo-osmolar plasma state, then steps should be taken to find the cause of this, for example, using CT to rule out pituitary tumour, and chest X-ray to rule out pulmonary tuberculosis or lung cancer. The mainstay of treatment in the non-acute stage is in the restriction of fluids. We find the method of target weight in the procedure described by Goldman & Luchin (1987) (and Delva & Crammer (1988)) to be useful in the management of other patients with water intoxication. Other methods such as oral sodium and high-dose propranolol (Shevitz *et al*, 1980) have been described. If medication proves to be an exacerbating factor, it should be adjusted.

To prevent missing the diagnosis, blood and urine should be taken for tests, even though measurement may not be immediate. In this case, the patient should have been admitted to the intensive-care unit rather than the general medical ward. In the face of such severe pulmonary oedema she should have been intubated, and intermittent positive-pressure volume with a volume-cycle respiratory should have been used. Venesection and the use of peritoneal dialysis should have been considered. The prognosis here was poor because of the underlying heart disease.

The hyponatraemic seizures can be managed with intravenous anticonvulsants if necessary. The correction of the sodium deficit with hypertonic saline has been described by Rendell *et al* (1978) but this can prove to be dangerous, as rapid correction of the hyponatraemia can cause demyelination of the pons. It is safer to use fluid restriction to allow the hyponatraemia to resolve gradually while supportive measures are used.

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Symptomatic Trans-sexualism

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A 24-year-old male schizophrenic had a delusion that he was female and had lived his life as a woman for almost two years. Unlike the only other reported case, his 'symptomatic trans-sexualism' responded to the effective treatment of his schizophrenia.

Ideas of sexual metamorphosis have received little attention in the literature, despite the claims of some authors that they are an invariable and pathognomonic feature of schizophrenia (Macalpine & Hunter, 1955). The only studies of note are those by Gittleson & Levine (1966) and Gittleson & Dawson-Butterworth (1967) who found delusions of sex change in approximately 25% of controlled samples of 57 female and 70 male schizophrenics. There are few individual case reports and, in particular, only two patients have been described in which delusions of sex change have been associated with cross-dressing (Akhtar & Thomspon, 1980; Newman & Stoller, 1974). Such cases of 'symptomatic trans-sexualism' have important implications for the management of trans-sexual patients. Here we present a further case and emphasise the need for caution in assessing individuals who request sex reassignment surgery.

Case report

W is a 24-year-old Jamaican man with no previous history of physical or psychiatric illness. At the time of his referral, he was in a local prison awaiting a court appearance on a minor charge of wilful damage. The reason for his detention was unrelated to the presenting complaint that he believed himself to be a woman.

On assessment, the most striking feature of his mental state was the fixed delusion that he was female. He was adamant that his penis was a vagina and when asked about his previous heterosexual relationships, said that he was a lesbian. His manner was effeminate and once released from prison he dressed in a skirt, blouse, and high-heeled shoes. His speech had a 'Shakespearian quality' to it and revealed schizophrenic thought-disorder. His response to a question about his self-image was "I see myself as what I do see and nothing else, I see myself as within the right and not the wrong", and when asked directly "are you a woman?" he replied "let me answer that by saying, when you say that you mean several assumptions . . . when that sounds right I don't know . . . am I sensible of it". There was no evidence of any other delusions, passivity experiences, or perceptual abnormalities. He did not appear unduly cheerful or depressed and was said to be eating and sleeping well. His cognitive function was normal. He did not believe himself to be ill, nor did he feel that his experiences were unusual in any way.

W's father said that his son had been dressing and behaving like a woman for over a year. He felt that W had been neglecting himself during this period and, in particular, was concerned that W was not receiving his social security payments because he had insisted on changing his name to that of a woman. He did not know of any family history of psychiatric illness and felt that W was behaving like a woman to imitate his mother, who had died two years previously of cancer.

W was born in Jamaica following an uneventful pregnancy and delivery, and came to the UK at the age of three months. As a boy he had a poor relationship with his parents and at school was described as a loner. He left with no qualifications and apart from a few brief part-time jobs and a year on an employment training scheme has not worked. He has had two major relationships, both heterosexual, and has consistently denied any sexual attraction to men. His first relationship lasted from the age of 16 to 22 when he lived with a woman by whom he has one son, aged five years. After she left him he married another woman but was divorced within a year because of his bad temper. Since then he has lived alone. He acknowledged occasionally using cannabis and at times drinking heavily but denied abusing any other drugs and said he had not suffered from withdrawal symptoms or memory disturbance with his drinking.

A diagnosis of schizophrenia was made applying DSM–III–R criteria (American Psychiatric Association, 1987) and after being fined and released from prison, W was seen as an out-patient and treated initially with fluphenazine decanoate in high dosage every 14 days. Two months later his delusions had resolved and he was no longer thought disordered. He had returned to using his original name and wearing male clothing and had, in general, reverted to approaching life as a heterosexual male. He currently continues to function well on a maintenance dose of fluphenazine decoanate, almost two years after the original diagnosis was made.

Discussion

Delusions of sex change are reported to be more common in unmarried schizophrenics, particularly males, but otherwise no clear relationship has been demonstrated between their occurrence and factors such as age and sex, duration and subtype of schizophrenia, and change of interest in sex (Gittleson & Levine, 1966; Gittleson & Dawson-Butterworth, 1967). There are four categories: delusions of no longer being a man, delusions of being a neuter, delusions of being both sexes simultaneously, and delusions of being of the opposite sex. Of these the latter have received most attention, partly owing to the issue of sex reassignment surgery (Newman & Stoller, 1974) but also because they have been the focus for debates about the relationship between trans-sexualism and schizophrenia (Hyde & Kenna, 1977).

Delusions of sex change as well as delusions concerning the size and shape of the genitals can be associated with genital hallucinosis (Gittleson & Dawson-Butterworth, 1966). This can take the form of simple sensations such as burning, or the patients may feel that people are invisibly masturbating them or attempting intercourse with them. Forty-four per cent of female and 30% of male schizophrenics in the studies of Gittleson & Levine (1966) and Gittleson & Dawson-Butterworth (1967) acknowledged having some kind of genital sensations. Olfactory and gustatory hallucinations are also reported to occur more often among schizophrenics who display delusions of sex change than those who do not (Connolly & Gittleson, 1971).

In our experience, delusions of sex change presenting as floridly as in the case we describe are uncommon. This is supported by the lack of similar cases described in the literature. Of the two previous reports where delusions of sex change have been associated with cross-dressing, only one involved the patient, a male, living openly as the opposite sex and he did not respond to antipsychotic medication (Akhtar & Thompson, 1980). The rarity of such presentations seems difficult to reconcile with the high prevalence of delusions of sex change reported by Gittleson & Levine (1966) and Gittleson & Dawson-Butterworth (1967). However, none of their patients spontaneously complained of such delusions or cross-dressed, suggesting that their phenomenology was less overt than in the patient we describe. Delusions of being of the opposite sex are still thought to be experienced by as many as one in five schizophrenics (Lothstein & Roback, 1984). We suspect that many of these cases go undetected and stress the importance of enquiring about sexual beliefs in psychotic patients.

Although florid presentations of delusions of sex change are unusual, particular care is required when assessing patients who request 'sex-change operations'. It is essential to rule out serious psychiatric disorder in these cases (Mate-Kole & Freschi, 1988) and it is worth noting that the only other reported patient who lived openly as the opposite sex because of his delusion (Akhtar & Thompson, 1980) was 'successful' in obtaining sex reassignment surgery.

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Erotomania in Relation to Childbirth

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A case of erotomania in relation to childbirth is reported. There was a good response to treatment and no evidence of relapse at 18-month follow-up.

In de Clerambault's syndrome (erotomania) the subject suffers a delusion of being in amorous communication with a person of higher rank who they believe was the first to fall in love and to make advances. The onset is sudden. The object of the amorous delusions remains unchanged but the subject provides an explanation for the paradoxical behaviour of the loved one. The course is chronic and hallucinations are absent (Enoch & Trethowan, 1979). De Clerambault (1942) defined the syndrome as primary ('pure erotomania') when it occurs in the absence of an associated psychiatric illness, and he also described a secondary form (Ellis & Mellsop, 1985).

Ellis & Mellsop (1985), however, found that most of the 58 cases of erotomania they reviewed occurred in the context of a diagnosable psychiatric illness (often schizophrenia or affective illness), and therefore argued against the existence of a primary form. They included reference to eight cases reported by Doust & Christie (1978), seven of which followed 'specific triggers', including drugs, brain disease, and psychological factors. Erotomania associated with senile dementia of Alzheimer type (Drevets & Rubin, 1987), organic affective disorder (Signer & Cummings, 1987) and organic delusional syndrome (El Gaddal, 1989) have been reported more recently. In this paper, we describe the first case of erotomania in which pregnancy and childbirth were important aetiological factors.

Case report

In July 1987 Mrs A, a 40-year-old mother of two children (aged 12 and 3½ years), was admitted to a psychiatric ward via a community psychiatric clinic. When pregnant with her second child (a daughter) she had visited her general practitioner (GP) (Dr B) for antenatal care. At these clinic visits Mrs A had felt there was a definite 'chemistry' between herself and Dr B and when she saw him five days post-partum, she believed that the 'magnetism' was still there. The next day he 'communicated' by telephone, although no one spoke. Ten days post-partum, Mrs A had symptoms of mastitis and was examined by Dr B "in a slow and lingering way". She now 'knew' he was in love with her. Over the next three-and-a-half years she continued to 'receive messages' (mostly professions of love and meeting arrangements) from him, via radio and newspapers and by the 'pinging' of her telephone. In reply, she sent record requests to the local radio station, and contacted him directly by telephone, by visits to his surgery and by many passionate letters. She had difficulty sleeping and suffered from a poor appetite, losing 9 kg over the next 18 months. She kept 'rendezvous appointments' and, although angry, made excuses when Dr B did not meet her. She came to believe that the radio presenters were passing offensive remarks about her. A non-smoker and never a heavy drinker, she drank two cans of beer most nights in the six months before referral.

She had had no previous psychiatric illnesses. At age two-and-a-half she had polio which left her with a limp and at age five she had pneumonia. Because of these illnesses, she was aged seven when she started school, where she was teased about her limp. She left school at 16 and did shop and clerical jobs. She described herself as shy, with feelings of inferiority, which she attributed to her limp. Her interests included history, mythology and flower arranging.

Her father, a 65-year-old retired miner, was regarded as a very intelligent and well-read man. Her mother, a 66-year-old retired pottery worker, had been treated for depression 24 years previously. Her brother, aged 38, was well.

She married at 26 after a five-year courtship. Her husband, three years her junior, was a painter and decorator. They had a good relationship, although she was dominant. He suffered from depression in 1981, and was treated by his GP. During Mrs A's unplanned second pregnancy, he had wanted, for financial reasons, to sell the new house they had just bought, but Mrs A would not agree. He had to do extra work to pay the mortgage. He became anxious and irritable and disharmony developed in the marriage. As the psychosis progressed, their previously satisfactory sexual relationship deteriorated. She lost feelings for her husband. He noticed that she became 'less committed', and that she began, without explanation, to insist on having the lights off during sexual intercourse.

Her two pregnancies were uncomplicated, and both daughters were delivered vaginally at full term, the first assisted by forceps. In spite of delusions occurring shortly after the second birth, Mrs A related well to the new baby, her health visitor (unaware of the psychosis) noting that she handled the baby confidently and competently. Mrs A did fantasise, however, that 'under different circumstances' her baby might have been Dr B's.

At interview, she was well groomed and her behaviour was normal. Her speech was spontaneous and normal in form, rate and tone. Her mood was normal and she was fully orientated. She had no insight into the elaborate system of delusions decribed above. There were no other psychotic phenomena.

She was started on trifluoperazine, increasing gradually to 15 mg t.d.s. She attended daily ward group meetings. Her delusions resolved slowly and she stopped contacting Dr B. After two months she was discharged and 18 months later this improvement was maintained and she had not contacted Dr B again.

Until the day of admission her husband had not known about her delusions or the resultant behaviour. He had not understood the change in their sexual relationship, nor had he investigated why the family had been removed from Dr B's list (18 months into the illness). He was very distressed and was helped by short-term intensive counselling.

Discussion

Like so many other cases in the literature, our case does not fulfil all the criteria derived from de Clerambault (1942) by Ellis & Mellsop (1985) because it did not have the sudden explosive onset which de Clerambault believed characterised pure erotomania. She meets the DSM-III-R (American Psychiatric Association, 1987) criteria for delusional disorder, erotomanic type, and the diagnosis using ICD-9 (World Health Organization, 1978) is paranoid state, simple.

Although puerperium is a time of greatly increased risk of psychosis (Kendell *et al*, 1976), these are mostly affective illnesses (Platz & Kendell, 1988), and paranoid psychoses with systematised delusions are less common in puerperal than non-puerperal psychosis (Brockington *et al*, 1982). Yet the aetiological importance of pregnancy and childbirth in this case can hardly be doubted. The unplanned second pregnancy shortly after moving house created financial and marital strain. The depression-prone husband, even though he would have preferred to move to a cheaper house, had to take on extra work. Consequently, he was less available to give Mrs A psychological and practical support in the last trimester of pregnancy, a time characterised by emotion and anxiety (Cox, 1979). Lacking this support she transferred feelings from her earlier relationship with her idealised father to her caring and competent GP. This transference of late pregnancy probably acquired its delusional quality in the first weeks post-partum.

Doust & Christie (1978) listed some 'triggers' for secondary erotomania, and other authors have found that an associated conventional psychiatric or organic diagnosis is appropriate in most other cases (Ellis & Mellsop, 1985; Drevets & Rubin, 1987; Signer & Cummings, 1987; El Gaddal, 1989). The theory that erotomania is of a secondary nature receives further support from this case history in which the psychological and social stressors, acting on a vulnerable personality, were catalysed by the physiological 'trigger' of pregnancy and childbirth and resulted in psychosis.

Acknowledgements

We wish to thank Professor John Cox for permission to report this patient and for his helpful comments on the manuscript.

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Anorexia Nervosa and Baby Gazing

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The uncommon behaviour of baby gazing is described in a patient who had also suffered three episodes of anorexia nervosa. The baby gazing responded to joint therapeutic interviews leading to the patient and her husband resolving their different views about having a family and the patient becoming pregnant. Even then there was a minor recurrence of anorexic behaviour which yielded to treatment.

The stealing of a newborn infant from a maternity ward is an offence likely to lead to wide publicity and police involvement. We report on a patient with anorexia nervosa, who visited hospital maternity wards to gaze at babies. Although this caused much anxiety among hospital staff and resulted in court injunctions, the woman did not actually steal a baby. Later, at the confirmation of her own pregnancy, this activity stopped but anorexic symptoms recurred in the first trimester of pregnancy. We propose the term 'baby gazing' to describe the hospital visiting, which has not previously been reported.

Pregnancy is rare in anorexia nervosa as conception is uncommon at low weight. Fantasies of pregnancy have been described in non-menstruating anorexic patients (Waller *et al*, 1940). In recovered anorexic patients who do resume menstruating and conceive, pregnancy appears to be a vulnerable time; average weight gain during pregnancy is often less than the minimum recommended, resulting in intrauterine growth retardation (Treasure & Russell, 1988). Anorexic symptoms can recur both during pregnancy and also after delivery (Weinfeld *et al*, 1977; Strimling, 1984) and may even present for the first time during pregnancy (Foster & Jenkins, 1987). According to these reports the critical time for the development of anorexic symptoms is towards the end of the second and early in the third trimester of pregnancy.

Case report

Mrs A was referred to the out-patients department of the Maudsley Hospital in September 1985, and said that her main problem was a desire to visit hospital maternity wards to look at babies. She was then aged 22 years.

The patient had an initially happy and uneventful childhood and was affectionate to her two younger siblings. When she was ten years old, she became gradually more disruptive at home but more withdrawn at school where she persistently claimed to be an adopted child. Her behaviour improved after behaviour therapy sessions at a local child guidance clinic and it was noted that no precipitant had been found. There was no family history of psychiatric illness.

Menarche was at 14. One year later she became convinced that she was fatter than the other girl gymnasts at school and began dieting despite having a weight of 49 kg (25th centile) and an average height (50th centile). Her weight fell to 38 kg (below 3rd centile) and menstruation ceased. Her family did not request medical help; instead her father forced her to eat and forbade any social activity. Her weight rose to 47 kg (Fig. 1).

Her first sexual relationship was at 17 with her first boyfriend. She recalls this as traumatic and despite not having mensturated since regaining weight, became convinced

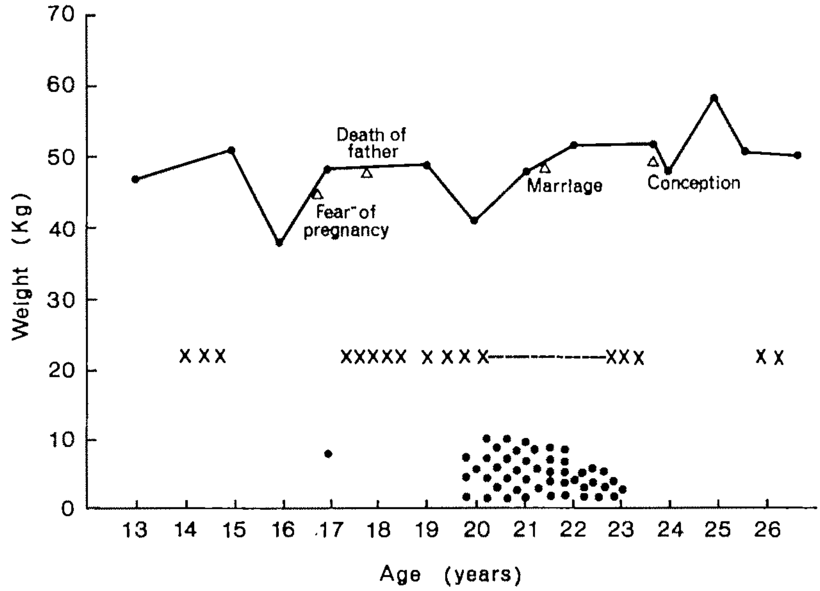

Fig. 1. Graph showing weight change with age (●——●) and life events (△), menstruation (×) (×—× signifies use of contraception), and incidents of baby gazing (● indicates approximate frequency of baby gazing).

she was pregnant. After she had taken a urine specimen to the hospital pathology laboratory she suddenly wished to see a newborn baby and went to the maternity ward and just gazed at the babies. On her way home she purchased a pair of white knitted bootees. When the test later proved negative she denied being disappointed or relieved, but ended the relationship with her boyfriend and devoted more time to her 'A' level studies. She was pleased when menstruation resumed shortly afterwards.

Later that year, the patient's father, an engineer, collapsed and died from aortic stenosis while at work. Her mother never encouraged any discussion of his death but the patient has on occasions talked of her father as though he were alive and mentioned him attending her wedding to Mr A. After leaving school at 18 the patient worked as a cosmetic consultant, again becoming more conscious of her appearance. She lost 8 kg by dieting, inducing vomiting after eating and abusing laxatives, and her menstruation became irregular. She was admitted to a medical ward and began eating but discharged herself after one week. At home she was able to gain weight with family encouragement.

During her recovery from this second episode, the patient began to visit maternity wards on a regular basis (Fig. 1). During a visit she would enter the ward, gaze at the babies and occasionally touch one. She had been reluctant to leave wards on request and at times had been escorted out by police. On two occasions she had picked up a baby in full view of mothers and staff and had carried it towards the ward exit but had returned it when asked. The patient denied any compulsion to visit maternity wards or any planning of visits. She strongly denied ever wishing to harm or steal a baby. She remained indifferent to the risk of prosecution even when an injunction had been served against her by one health authority. She never exhibited any psychotic features and there was no link between the baby gazing and a sustained depressed mood.

She was referred to local psychiatric services where at initial assessment she gave a complicated history. She claimed to have suffered a stillbirth at 17 years, had two subsequent miscarriages, and to be worried about her fertility. She had never pretended to family or friends that she had ever been pregnant, nor at any time believed herself to be. Her general practitioner confirmed that she had never been pregnant. When her fiancé later challenged her about the alleged pregnancy in the presence of medical staff she said she had meant this as a joke. Since she did admit to a low mood, a diagnosis of depression was made but she did not comply with the prescribed medication. Her mood improved spontaneously within three weeks and she was able to explore some of her feelings with a psychologist. These sessions ended when Mr and Mrs A moved into the London area when Mrs A was 21 years old.

At the time of referral, Mrs A had access to over 20 hospitals in London and the south-east England area, and was visiting some of these three to four times each week, either in the evening or on days off from her work as a receptionist. She had also visited private maternity wards where she was able to obtain a conducted tour of the facilities by claiming to be 10 weeks pregnant. She had amassed a large collection of books about baby care, collected free samples of baby lotion and shampoo, and kept a large white rabbit in the living area of her home which she talked to as though to a young child. She was maintaining her weight below a self-imposed threshold of 51 kg but was eating a normal diet and not vomiting or abusing laxatives. On occasions, she required reassurance that she was not overweight which Mr A, a customs officer six years older than Mrs A, provided. Mrs A claimed the marriage was completely happy, but Mr A felt he was becoming less tolerant of his wife's behaviour and was both embarrassed and concerned at the effect the resulting police involvement would have on his job. Their sexual relationship was regarded as fulfilling by both.

Management of the problem was first aimed at reducing the baby gazing as there was concern that she might actually attempt to steal a baby. A community nurse visited their home and Mr A was advised in behavioural techniques and limit setting. In regular out-patient appointments with a registrar, and in consultant supervision, Mrs A's behaviour, motivation and feelings were discussed. Mrs A explained that at the times she baby gazed she did feel in need of some comfort and support, but her only admitted motive was to relieve boredom. She remained indifferent to the effect of her behaviour on the babies' mothers and its consequences for her husband. Exploration of feelings about her father's death centred on acceptance of loss.

At subsequent joint appointments, Mr and Mrs A concentrated on their future plans as a couple. Mr A favoured delaying pregnancy because of his concern over their financial security. Mrs A initially said she would like five children, before rationalising that they would be "brought up in poverty which isn't fair". She also claimed that she would not be concerned about gaining weight during pregnancy: "when you're pregnant it's different . . . getting heavier – it's a baby, not fat". Discussion of other topics was encouraged so that the focus of attention moved away from baby gazing.

Mrs A's baby gazing gradually decreased over the following six months. During this time Mr and Mrs A decided to have a child of their own and Mrs A actually stopped baby gazing once her own pregnancy was confirmed.

In the eighth week of pregnancy, Mrs A's weight began to decrease in association with some morning sickness. She then started to restrict her food intake so by the 14th week she weighed 3 kg less than at the time of conception. She denied wanting to lose weight but was extremely concerned with her changing shape and exceeding her self-imposed weight threshold. Mrs A's weight was monitored at frequent out-patient appointments also attended by Mr A. He was encouraged to supervise meals and record a daily caloric intake, aiming for at least 2000 calories per day. Pelvic ultrasound scans showed satisfactory foetal growth and Mrs A had gained 7.5 kg at term. A girl was born by normal delivery, weighing 3.4 kg (50th centile), head circumference 35 cm (50th centile). Although Mrs A had some post-natal depression, her scores on the Edinburgh Post-Natal Assessment Scale (Cox *et al*, 1987) at four, six and eight weeks were within normal limits.

Since the birth, Mrs A has maintained a healthy weight of 50–51 kg, is eating a normal diet and has resumed menstruating regularly. The baby is developing normally and weighs just below 50th centile. Mrs A has not resumed her baby gazing.

Discussion

Mrs A's baby gazing occurred with greatest frequency when she was amenorrhoeic because of low weight and also when taking the contraceptive pill (see Fig. 1). These situations could be regarded as 'self-induced' infertility. One speculation is that the first baby-gazing incident represented an initial wish for pregnancy; the more frequent baby gazing that occurred later was the result of her suppressed desire for pregnancy in order to comply with her husband's financial argument against pregnancy. Baby gazing stopped when they had both agreed on their wish for a baby and Mrs A's pregnancy was confirmed.

This explanation may be too simple: psychoanalytical theories seeking to explain anorexia nervosa and infertility suggest a fear of oral impregnation (Waller *et al*, 1940), and anorexia nervosa in a woman who apparently wants a baby could also be regarded as a resolution of conflict about pregnancy. At the time she was baby gazing we suspected Mrs A of wanting a baby although she did not admit to this. She demonstrated considerable ambivalence about pregnancy: although she had a large collection of baby-care books, she justified this only as a topic of interest to her; while actually baby gazing, she would repeat her husband's financial argument against pregnancy to staff. Mrs A's baby gazing can therefore be considered as a displacement activity which illustrates her own indecision and ambivalence.

Frankiel (1985) has suggested that the wish to steal a baby is a wish to replace parents and rescue the child. This issue was addressed in a 15-year-old girl with a persistent desire to steal a baby who responded well to psychoanalysis (Moore, 1976). d'Orbán (1972; 1976) argued that for some women who actually steal babies and children the motive is comfort whereas in others it is an attempt to manipulate their partner. The former group tend to steal children that they know, have strong desires for children, and tend to be separated from their own children. Some women claimed their offence occurred after a miscarriage but this was not always verified by obstetric histories and less than half of the women had proven fertility at the time of the theft. Although Mrs A had claimed to have suffered a stillbirth, there was never any evidence of pseudocyesis which has been reported in association with baby stealing (d'Orbán, 1982). Her baby gazing appears to be more similar to the comfort-seeking aspect of d'Orbán's child stealers while hysterical mechanisms may have been important in her claims of pregnancy and stillbirth as well as in the denial of her father's death.

The outcome for women who actually steal babies or children appears to be unfavourable as three of 14 women in d'Orbán's series were reconvicted. However, our patient actually stopped baby gazing at the confirmation of pregnancy. d'Orbán (1982) also reports that one child stealer who received in-patient psychiatric treatment as a condition of probation improved six months after her own baby was born.

Prior to pregnancy, Mrs A appeared to accept the inevitable weight increase and shape change. However, a recurrence of anorexic symptoms resulting in weight loss was detected during the first trimester. As Mrs A was then encouraged to increase her caloric intake her subsequent weight gain at term was satisfactory and she produced a healthy baby.

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Editor: Ian Pullen

Contents: Predicting the productive research psychiatrist/Relevance of research for clinical practice/Anticholinergics: the consensus statement/Multiple personality disorder/ECT for pseudodementia/Psychiatry and ethnic groups/HDL-DR2-frequencies in affective disorders/Clomipramine for OCD/Unmet needs for medical care/Glucose metabolic rate in schizophrenia/Failure of progesterone treatment in puerperal mania/Post-traumatic stress disorder.

Predicting the productive research psychiatrist

SIR: I read Parker's article (*Journal,* January 1989, **154,** 109–112) with considerable discomfort as it seemed to fail both scientifically and morally in claiming that the most important predictive factor for the productivity of a research psychiatrist was 'track record', contributed to principally by "the number of publications in the early part of the review period, number of citations to published work, rating by peers, and possessions of a research degree". It is quite obvious to me that the most important factor is the sex of the psychiatrist, i.e. one should be male and then other factors follow. While I would not dispute that Professor Parker had a representative sample of psychiatrists, the fact that there is a male preponderance (89%) suggests that sexist prejudice plays a critical role. The establishment, which is male, seeks representatives like itself to propagate it. Women are largely left out, or are given assistant status, e.g. Professor Parker mentions women at the bottom of the paper where grateful thanks are given in small print.

Unfortunately, sexual stereotyping is still prevalent among both male and female medics. Moreover, the UK government, having committed itself to educating equal numbers of male and female medical students, found that self-regulation of the medical profession and its institutions could not be relied on to achieve this and thus commissioned a study to examine the main influences on the careers of women doctors (Allen, 1988). This reported that medical career progress depends on an 'old boy network' which excludes women (Allen, 1988). Thus, women have to spend longer periods at each grade and experience worse career prospects. They are also expected to specialise in less prestigious medical specialities. To make the matters worse many medical women still have a lower degree of confidence than men (although higher then ten years ago) and unrealistic expectations of what they should be doing, so that they commit themselves to too much work i.e. they still do more than their share at home. This, of course, means that too little domestic responsibility is taken by the majority of (medical) men who expect even a professional spouse to lapse into a domestic role to facilitate the fast progress of the man's career.

There are many papers on attitudes to women in science and Professor Parker might say that these are only published in trivial journals. I would like to remind Professor Parker that every reputable journal has been trivial at some stage of its existence.

There is no such thing as an absolute everlasting security for any establishment, and the fear of change can lead to behaviour which creates entry barriers for the newcomers in the form of rules and regulations which are oppressive, limiting to progress and ultimately detrimental even to the authors of such rules. Thus, it is important to recognise that there are destructive psychosocial factors which are much more important in determining the productivity of a research psychiatrist than it is pleasant to admit. Alternatively, one could say that the social system itself positively reinforces the careers of some people more than others.

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SIR: In a polemic that has a distinct *ad hominem* tone, Haeger imputes poor science, failed morals, prejudice, sexism, condescension and a dismissive capacity (moi?).

I suggest that Dr Haeger confounds issues of access to a research career and 'success' within that field. In a similar way, a colleague once complained about the rejection rate of submissions by women after observing that female authors were in a minority in our regional journal. I reviewed the data for a nine-year period and found that, as suggested, a minority of published articles were by women, but that they submitted only a minority of papers. In fact, the acceptance rate for articles was higher for women. Similarly, I have now reviewed the 'research productivity' data set under discussion and report that the female researchers were responsible for a mean of 3.5 papers, compared to a mean of 4.2 for male researchers, over the period of audit. While there were too few women in the sample to interpret such analyses formally or confidently, that finding suggests that productivity rates in this region are unlikely to differ very much between male and female psychiatric researchers.

The central finding from the study – that productivity is best predicted by 'track record' variables – would require examination in a data set with separate and sufficiently large sub-samples of male and female researchers, to determine if the prediction holds true for female as for male researchers.

While my sample was carefully generated (see Parker, 1986) to ensure that all potential researchers in the region, male or female, were included, the marked male preponderance (89%) exceeds the current RANZCP College membership rate of 79% being male. Thus, I suggest that, while the sample was 'representative' of the active research community, it was not representative of the overall sex ratio of psychiatrists in this region, clearly suggesting that fewer women are engaged in research.

Thus, sex is relevant in 'joining' the psychiatric research community, but it remains to be established whether it is a predictor of productivity or related to other outcome variables or performance indicators within that community, and it must be kept in mind that my focus was on the latter issue, not on the issue of access.

Dr Haeger may be right in drawing attention to the negative consequences of sexual stereotyping and to the other problems faced by female psychiatrists in gaining access to, as against 'success' in, a research career, and certainly such difficulties are recognised in relation to in obtaining academic posts. But it remains (to my mind) to be established that a research career *per se*, or even engaging in research, is affected by sexual prejudices, particularly when psychiatric research is commonly a part-time activity. It could also be that a career in research is regarded as less relevant, attractive and pleasing to women for a host of reasons, so that fewer seek such a career or job option. A survey of trainees and an ethnographic study of male and female psychiatric researchers might be of interest in examining a number of the propositions underlining Dr Haeger's polemic.

Implicit in Dr Haeger's letter is a view that research is an elitist field. For those who encourage junior staff to consider research (and observe eyes glaze over) and for researchers who live to the financial and other limitations of such a career, that may be news.

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Relevance of research for clinical practice

SIR: I read with interest Paykel's Maudsley Lecture reviewing the relevance of research on the treatment of depression for clinical practice (*Journal*, December 1989, **155**, 754–763), but was surprised that he neglected completely three aspects of well recognised treatments for depressive illness: lithium carbonate as a prophylactic (Abou-Saleh & Coppen, 1983); lithium carbonate augmentation of antidepressant drugs in resistant cases (Heninger *et al*, 1983; de Montigny *et al*, 1983; Schrader & Levien, 1985) and psychosurgery. I hope Professor Paykel will at some stage address this point.

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SIR: Dr Al-Sheikhli correctly points out that I omitted from my Maudsley lecture three useful treatments for depression. In my preamble I indicated my intentions particularly to review choice among treatments and also to illustrate the two-way relationship between research and clinical practice. The field is large and I had perforce to limit myself to five common treatments. Each was chosen because there existed a large number of published treatment studies and because it exemplified some aspect of the interrelationship between practice and research. Lithium carbonate is well established as a prophylactic treatment for bipolar manic-depressive disorder and some unipolar patients certainly could have met my criteria for inclusion. Lithium augmentation is undoubtedly valuable but there have been fewer controlled studies. Psychosurgery also has a place in severe resistant depression although here, more conclusive research regarding efficacy and indications is still needed. This might be something which the College itself could take up: I understand that the Mental Health Act Commission has comprehensive records of patients who have received psychosurgery since the new Act.

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Anticholinergics: the consensus statement

SIR: We are grateful to Barnes for his comment (*Journal*, March 1990, **156**, 413) on our consensus statement (*Journal*, March 1990, **156**, 412), because it gives us the opportunity to provide some information on the purposes and the underlying rationale of the series of such statements that our group is currently producing.

These papers approach some highly controversial topics in clinical psychopharmacology, providing for each a concise outline of the different views expressed in the literature and a list of recommendations agreed upon by all the members of the group.

The statements are directed not so much at researchers or experts in the field as at the large audience of clinicians working in psychiatric wards, out-patient units or community services. This is why they are very brief, without any data or even references: in fact, it is our experience that very busy practitioners prefer this format.

The aim is not, therefore, to provide an exhaustive review of the literature or of the opinions of different authors and their empirical support. Furthermore, it should be stressed that the statements are designed for worldwide dissemination (each of them will be translated into several languages), and the recommendations are aimed at psychiatrists in developing as well as industrialised countries.

Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment was found to be a suitable topic for a consensus statement because: (a) the views expressed in the literature about this issue are very discordant; and (b) it is important for the World Health Organization (WHO) to receive a clear input about the usefulness of a class of medications which are largely prescribed to psychotic patients in industrialised countries, but have never been included by the WHO in the list of essential psychiatric drugs.

In order to produce the statement, several discussions were necessary since opinions were initially divergent within our group. We are not surprised, therefore, that Dr Barnes' views are not in perfect agreement with our final consensus. In this sense, we see Dr Barnes' comment as an addition rather than as a criticism of our statement and welcome it without any reservation.

The comment expands some of the points made in our paper, adding details and references. Dr Barnes argues that, on the basis of the available literature, "the issue seems to be far from resolved". He is perfectly right: actually, in the presence of an agreement in the literature, the topic would have not been selected.

We agree with Dr Barnes' points that some of the hazards and side-effects of anticholinergic drugs listed in the document, such as the contribution to hyperthermic episodes and the antagonism of the therapeutic effects of antipsychotics, "are relatively uncertain", and that short-term prophylactic use of anticholinergics in the early phase of neuroleptic treatment may sometimes be useful. His formulation amplifies the cautions already present in the statement.

According to Dr Barnes, "the statement suggests that short-term prophylactic treatment is particularly useful to avoid the development of akathisia". Clearly, we were not sufficiently explicit: our document simply mentions, when listing the arguments in favour of prophylatic treatment with anticholinergics, that these drugs have been *claimed* to be useful in avoiding the appearance of neurological manifestations (such as akinesia and akathisia) which may mimic psychopathological symptoms and therefore lead to an inappropriate increase of the neuroleptic dosage (see Kane, 1988). It is not surprising, however, that Dr Barnes, who rightly points out that anticholinergics have "an uncertain reputation" in akathisia, concludes that "one explanation for the positive perception of anticholinergic drugs by the patients may be that they relieve the discomforting experience of bradykinesia or *akathisia* associated with antipsychotic medications".

That "the relative liability for Parkinsonism of the various antipsychotic drugs available cannot be confidently predicted" is clearly Dr Barnes' personal opinion. A large literature (see Tamminga & Gerlach, 1987) presently supports the view that drugs such as clozapine, sulpiride or thioridazine are much less prone than high-potency neuroleptics to produce extrapyramidal side-effects. Finally, the relationship between anticholinergic treatment and the development of tardive dyskinesia is certainly debatable, but, as the discussant himself recognises, the experimental and clinical evidence supporting a predisposing role of anticholinergics is compelling, and it would have been irresponsible for us to ignore it.

In conclusion, we welcome Dr Barnes' comments although they do not lead us to propose changes in the document's recommendations.

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SIR: The WHO Consensus Statement (*Journal*, March 1990, **156**, 412) provides welcome guidance in view of the widespread use of concurrent anticholinergic antiparkinsonian and neuroleptic medication. Studies in Oxford, Birmingham and Newcastle have shown that 50–55% of patients are maintained on both drugs concurrently and, in some cases, for over 12 months (McClelland *et al*, 1974).

There are additional reasons for not routinely co-prescribing the two agents. A longitudinal survey (Johnson, 1978) demonstrated that Parkinsonian side-effects show marked spontaneous fluctuation, making the interpretation of the effects of treatment difficult to interpret. Moreover, in one study, a deterioration in schizophrenic symptoms was observed when an antichlorinergic antiparkinsonian drug was introduced (Johnston *et al*, 1983).

However, there remains a useful role for these antiparkinsonian anticholinergic drugs in certain areas of clinical practice. For example, many clinicians would consider prescribing both drugs concurrently in patients with a previous history of acute dystonic reactions. The statement failed to highlight the uncommon, but potentially fatal, complication of asphyxia secondary to neuroleptic-induced laryngeal pharyngeal dystonia (McDonal, 1981) or to oesophageal dysmotility (Moss & Green, 1982) which might be preventable in this way. Similarly it has been observed (Van Putten, 1974) that many patients dropped out of treatment as a result of drug-induced extrapyramidal disorders. Hence patients who have previously defaulted due to such side-effects may benefit from co-prescription.

The decision as to whether to use anticholinergic antiparkinsonian drugs may only be decided by a clinical assessment of the balance of risks. It is important to emphasise that once prescribed it is essential that the patient and the indications for such therapy are reviewed regularly.

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VAN PUTTEN, T. (1974) Why do schizophrenic patients refuse to take their drugs? *Archives of General Psychiatry*, **31**, 67–72.

SIR: Putting aside for a moment the *content* of the recently published WHO concensus statement on prophylactic anticholinergic medication (*Journal*, March 1990, **156**, 412), I would like to deliberate on the fact that a more conventionally laid out review appeared in the same edition (*Journal*, March 1990, **156**, 413). I wonder if this might in part be reflecting physicians' discomfort at being presented with conclusions rather than the more usual critical appraisal, and what would this imply for the 'reformed' National Health Service. The new emphasis on local management will bring doctors into much closer contact with the sort of skills seen in business, based often it seems on charisma, people-management ability and ideology, rather than the familiar (safer?) 'medical model' of a broad-balanced review and hypothesis testing. Could be a bit of a culture shock for all of us!

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Multiple Personality Disorder

SIR: Coons (*Journal*, March 1990, **156**, 449) and Ross (*Journal*, March 1990, **156**, 450) criticise Simpson's assertion that multiple personality disorder (MPD) is an "iatrogenic, largely culture-bound condition" (*Journal*, October 1989, **156**, 565). Professor Simpson may overstate the case for the iatrogenic component, but more striking is the readiness of Drs Coons and Ross, both prominent writers in the field, to dismiss this consideration out of hand. Dr Coons suggests that MPD occurs in all countries, but his evidence is anecdotal and is at odds with the experiences of clinicians in the UK. It is my view that the type of patient reported in the American literature is extremely rare in this country.

However, I would accept that short-lived dissociative reactions occur when patients insist for a limited period that they have assumed the identity of another personality. Indeed, it would be odd if such a presentation was not one of the almost infinite variety of dissociative reactions. The evidence in support of this assertion comes from my own clinical experience (Fahy *et al*, 1989) and from the recent paper by Adityanjee *et al* (1989) from India who report three patients with short-lived dissociation of personality. In the Indian cases, as well as our own, the symptoms were seen as stress related, and they resolved without attempting to interview the alternates at length.

It is my contention that these relatively benign reactions may not be uncommon, and are most likely commoner in patients with other neurotic or post-traumatic syndromes. However, to attain the complexity of psychopathology seen in American cases of MPD, some element of reinforcement from therapists, relatives or the media is necessary. MPD researchers have largely ignored this factor in their investigations. Instead, Dr Ross suggests that variations in diagnostic rates between countries may be a reflection of the differing rates of childhood trauma, a theory which is unlikely to be relevant in differences between the UK and USA and which is supported by no evidence whatsoever.

Finally Dr Coons falls back on the tautological argument that the comments of sceptical observers of the MPD scene are rendered invalid because they are not seeing large numbers of real cases. The problem with this argument is simply that sceptics may well be seeing these patients but are coming to different opinions on diagnosis. If the diagnosis of MPD is to gain widespread credibility, then it is up to workers like Drs Ross and Coons to provide evidence of conceptual validity through *controlled* trials studying aetiology and treatment of this enigmatic condition.

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ECT for pseudodementia

SIR: I read with interest the good review article by Benbow (*Journal*, August 1989, **155**, 147–152). Although Dr Benbow talked about the use of electroconvulsive therapy (ECT) in treating the patients who are demented as well as depressed, I was surprised that she did not mention the good response of ECT in 'depressive pseudodementia'.

The term 'pseudodementia' is a controversial one, but it is a fact that in some patients 'functional' depressive disorder may show intellectual impairments and memory difficulties resembling those of organic disorder. Pseudodementia is frequently encountered in elderly patients with the more severe kinds of affective illness (Post, 1982). Post reported that 10% of elderly depressed patients present with pseudodementia. The increased severity of depression could explain the good response of these patients to ECT.

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Psychiatry and ethnic groups

Sir: In their paper on police admissions to a psychiatric hospital, Dunn & Fahy (*Journal*, March 1990, **156**, 373–378) report that for both black and white patients, "treatment does not appear to be independent of diagnosis". We recently completed a survey (Lloyd & Moodley, 1990) in the Bethlem and Maudsley Hospitals of 138 catchment-area in-patients, comparing white patients of British origin with black patients of Caribbean origin, and found important differences as well as similarities in the treatment received by these two ethnic groups in terms of types, routes, and frequency of administration of psychotropic medication, diagnosis, detention under the mental health act, and episodes of violent behaviour, self-harm and absconding. Some of these differences were dependent on diagnosis, others were not.

Black patients of both sexes were more likely to receive a clinical diagnosis of schizophrenia (Yates' $\chi^2 = 3.91$). Black patients with a diagnosis of schizophrenia were more likely to be compulsorily detained than their white counterparts matched for age and sex (Fishers exact test $P < 0.05$). Black patients with a diagnosis of schizophrenia were more likely to have been involved in a violent incident during the index admission (Fishers exact test $P < 0.05$) whereas white patients were more likely to have been involved in an episode of self-harm.

Without matching for diagnosis, significantly more black than white patients received antipsychotic drugs (Yates' $\chi^2 = 6.351$, $P < 0.05$) and depot antipsychotic preparations ($\chi^2 = 8.96$, $P < 0.01$). When matching for diagnosis, age and sex, black patients with a diagnosis of schizophrenia were no more likely to receive antipsychotic medication either orally or by depot injection than their white counterparts.

The dosages of differing antipsychotic drugs given by various routes and frequencies were converted to their equivalents in daily milligrams of oral chlorpromazine using conversion factors derived from a number of sources (Lloyd & Moodley, 1990). Without matching for diagnosis, black patients received higher oral and depot dose equivalents than their white age, sex-matched counterparts ($P > |Z| = 0.04$). These differences disappeared when patients were matched for diagnosis.

White patients who had been involved in a violent incident or were detained under the mental health act received significantly higher doses of antipsychotic medication than informal white patients who had not been involved in a violent incident ($P > |Z| = 0.0080$). This was not the case for black patients who received similar doses of medication whether formal or informal, violent or not.

This suggests that black in-patients were more likely to receive antipsychotic medication, especially depots, because they were more likely to have a diagnosis of schizophrenia. The accuracy of those diagnoses is of central importance. Even if the diagnoses are correct, black patients with a diagnosis of schizophrenia were more likely to be detained under the mental health act than their white counterparts, and to have been involved in a violent incident. It could be argued that this reflects higher levels of disturbance among the black group. Alternatively this could be due to the predominantly white staff's perception of the dangerousness of the black in-patient group. One prevalent myth we discovered while conducting this study was that many of the black schizophrenics in the hospital were "big, dangerous and chronically psychotic". In fact, there were no statistically significant differences between the two ethnic groups for age, height, weight, length of stay, number of previous admissions or length of illness from first presentation. Speculatively, it may be that myths of this sort contribute to differential access to the services and to black patients receiving more coercive means of treatment.

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HLA-DR2-frequencies in affective disorders

Sir: Rieman *et al* (*Journal*, February 1988, **152**, 296) reported on HLA-DR2-frequencies in patients with endogenous depression (bipolar and unipolar type). Seven of 11 patients studied (64%) were DR2-positive compared with a population rate of about 16% (Albert *et al*, 1984).

Serologically-detectable HLA-DR-specifities arise from genetic variation at the DRβ_I-locus coding for the β-chain of the DR-antigens. Since DRβ_I-cDNAs have been cloned (Long *et al*, 1983) and can be used as hybridisation probes, RFLP patterns can be detected which correlate with known HLA-DR-specifities. As devised by Cox *et al* (1988), identification of most specifities is possible by analysis of RFLP patterns obtained after digestion of genomic DNA with the restriction endonuclease TaqI. There are only two exceptions: DR3 cannot be distinguished from DRw6, nor DR7 from DRw9 by this procedure.

In order to re-examine the hypothesis of a possible association of HLA-DR2 to affective disorders in a larger sample, we investigated 88 patients (53 females, 35 males) diagnosed according to DSM–III criteria (American Psychiatric Association, 1980). Fifty-seven of the patients had bipolar illness and 31 had major depression. Thirty-two showed a family history of affective disorders. Age-of-onset ranged from 14 to 64 years.

One hundred people recruited from medical students and medical and laboratory staff served as control probands, and those who had first-degree relatives with affective disorders or a personal history of psychiatric illness were excluded from the study. The female:male ratio was 51:49. All the subjects tested were Caucasians of European origin. The laboratory procedures followed standard protocols.

In our sample of patients with affective disorder, HLA-DR2 is less frequent (8%) than in healthy control probands (16%). The other DR-specifities were not different between patients and controls. Calculation of a 2×2 χ^2 statistic for the frequencies of HLA–DR2 in patients and controls even reaches borderline statistical significance ($\chi^2 = 4.245$; $P = 0.039$) without correction for multiple testing.

Obviously, our results do not confirm those found by Riemann *et al.* Since population association studies are well known to be affected by stratification effects, we would not claim a negative association of DR2 to affective disorders. In any case, we could not replicate the reported association of HLA-DR2 to affective disorders.

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Clomipramine for OCD

SIR: The points raised by Chiu *et al* (*Journal*, January 1990, **156**, 112–115) that clomipramine may be useful in treating delusions, and that there may be an association between monosymptomatic delusional states and obsessive–compulsive disorder (OCD), possibly involving an underlying abnormality in serotonin function, are not new.

Over the past few years ideas concerning the identity of OCD have been changing. Treatment studies in OCD, which consistently demonstrate a selective response to drugs with 5-hydroxytryptamine-(5-HT)-reuptake inhibitor properties and a failure to respond to other conventional antidepressants, anxiolytics and antipsychotic drugs (Montgomery *et al*, in press) suggest a distinct, principally serotonergic abnormality underlying the illness, and an identity separate from the anxiety disorders (with which OCD is currently classified in international diagnostic systems), from depression and from schizophrenia.

Phenomenological studies of OCD also indicate that some of the traditionally-accepted diagnostic criteria – notably the need to resist and to be constantly aware of the senselessness of the symptoms – may not be as important as previously thought. Patients who have been suffering with chronic obsessions and compulsions for many years often, understandably, lose the urge to resist (Stern & Cobb, 1978). The need for complete insight into the absurdity of the phenomena remains a rather more controversial subject. Again, patients with long-standing severe OCD may, at times, appear to fail to recognise the senselessness of their behaviour, while, at other times, may retain complete insight. Insel & Akiskal (1986) review a number of individual cases of OCD where a shift from 'obsessions' to 'delusions' was monitored as the illness became more severe and insight was lost. Interestingly, these 'deluded' patients still responded best to treatment with clomipramine.

The recent open reports of five cases of body dysmorphic disorder (DSM–III–R), where ideas about body deformities bordered upon the delusional in the absence of prominent depression, and where the patients responded to treatment with 5-HT-reuptake inhibitors in preference to a variety of other antidepressants and neuroleptics, are consistent with the proposal of a common serotonergic pathology underlying some monosymptomatic delusional disorders and OCD (Hollander *et al*, 1989). Depressive symptoms commonly occur as part of OCD, and the concept of OCD as a syndrome composed of a spectrum of symptoms including delusions has gained some recognition (Solyom *et al*, 1985).

However, open reports of drug responses are notoriously unreliable and it is a pity that Dr Chiu's cases also fall into this category.

Controlled investigation of non-depressed individuals with monodelusional states, examining the efficacy of 5-HT-reuptake inhibitors and neuroleptics, either alone or combined, are indicated to explore OCD and delusions more thoroughly.

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Unmet needs for medical care

SIR: Brugha *et al* propose a potentially useful concept in their paper on unmet needs for medical care in the long-term mentally ill (*Journal*, December 1989, **155**, 777–781). However, because of suspect methodology and inadequate evidence (at least as reported in the paper) it is impossible to accept their conclusions.

Firstly, in a paper discussing physical health and illness, it is difficult to understand the rationale behind not performing a physical examination on each patient. The authors acknowledge this, but do not attempt to explain it. Nevertheless, they claim the presence of dental or gum disease in 28% of those "who were examined".

Secondly, the authors make two quite unsubstantiated claims regarding the particular value of thyroid and liver-function tests and the finding that need for medical care was equally likely in users of non-hospital day services. They are obvious important implications for both these claims, but it is impossible to judge their merits without being able to examine the evidence underlying them.

The final, and perhaps most glaring omission, is the absence of any reference to the primary health care services. It seems highly likely that the level of unmet need for medical care in a defined population is highly dependent on the local primary care services. The knowledge, concern and skills of the primary care team, together with the liaison between the primary and mental health care teams, particularly regarding responsibility for the physical care of these patients, will surely influence the levels of unmet need in the population.

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Glucose metabolic rate in schizophrenia

SIR: A decrease in the glucose metabolic rate in the right frontal lobe in schizophrenics compared with controls (assessed by positron emission tomography during a continuous performance test) (*Journal*, February 1990, **156**, 216–227), and a significant reduction of mixed- and left-handedness in male epileptics with schizophrenia (*Journal*, February 1990, **156**, 228–230) suggest a protective role for lateralised brain function. This is supported by norepinephrine-induced exacerbation of schizophrenia (van Kammen *et al*, 1990), manifested by auditory hallucinosis during oculogyric crises (*Journal*, July 1989, **155**, 110–113 and October 1989, **155**, 569–570), which may be elicited by noradrenergic-mediated inhibition of dopamine lateralised to the right hemisphere (Rascol *et al*, 1989 and *Journal*, February 1990, **156**, 285). In contrast, compulsions were characterised by prolonged spin-lattice relaxation time on magnetic resonance imaging in the right frontal cortex (Garber *et al*, 1989), and auditory-visual hallucinations preceding oculogyric crises were perhaps induced by fatigue in a non-schizophrenic epileptic woman (Leigh *et al*, 1987).

Inter-relationships among mental and motor symptoms, including gaze and thought disorders, sequentially analysed on a time-base, handedness, gender, lateralised brain functions and detailed gyrus-by-gyrus analysis of the frontal lobe (*Journal*, February 1990, **156**, 216–227) may provide an understanding of how specific patterns of monaminergic overactivity lead to the cognitive disturbances that are clinically significant and a hallmark of schizophrenia (Braff & Geyer, 1990).

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Failure of progesterone treatment in puerperal mania

SIR: Progesterone is widely used in the treatment and prophylaxis of post-natal depression (Dalton, 1985). Sedative effects have been reported when this hormone is given intravenously (Merryman *et al*, 1954). If the onset of psychosis in the early puerperium is related to the precipitous fall in circulating progesterone after childbirth, progesterone therapy might be of benefit in early-onset puerperal mania.

We tried this therapy with three patients, all of whom expressed a preference to try hormonal therapy rather than neuroleptic drugs. The first patient, with a seven-day history of mania starting six days post-partum, reported a subjective calming effect with progesterone (50 mg intramuscular) before and after neuroleptic therapy was commenced. The second patient had suddenly become manic on day four post-partum; administration of progesterone (100 mg) on day six, and repeated after 12 hours, was associated with a surprising return to normality over 24 hours. She had, however, received chlorpromazine (50 mg intramuscular) and haloperidol (40 mg intramuscular) over the 24 hours before being given progesterone. These experiences suggested that intramuscular progesterone was well tolerated and might have an antimanic effect, and encouraged us to use it as the sole therapy in a typical case of puerperal mania.

The third patient had suddenly developed puerperal mania on day seven post-partum and had only been given oral chlorpromazine (100 mg) before progesterone was started. Progesterone (100 mg intramuscular, 12 hourly) was commenced as the sole therapy 12 hours after the onset of the disorder and continued for one week. A random blood level late in this week was 476 nmol/l (about average for levels in late pregnancy). There was *no effect at all* on her mental state with this regime. After switching to standard neuroleptic therapy, a significant improvement occurred within a few days. While we would not wish to discount the possibility of a beneficial effect of progesterone on the basis of one case, we think it important to give publicity to this definite therapeutic failure.

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Post-traumatic stress disorder

SIR: Medley *et al* (*Journal*, January 1990, **156**, 134) raise two important issues in relation to post-traumatic stress disorder (PTSD).

The debate over the relative importance of the trauma itself and pre-existing personality factors and psychological morbidity is likely to be around for some time to come. Of more immediate clinical importance is the diagnosis of PTSD in survivors of catastrophic accidents who have sustained significant head injury. DSM–III and DSM–III–R both indicate that the first criterion for the diagnosis of PTSD is that the individual has 'experienced' an extreme or catastrophically stressful life event. Survivors, such as those who survived the recent crash on the M1, who were immediately rendered unconscious and remained so while they were being rescued, would not have 'experienced' the event. It should not therefore be expected that they would satisfy the criteria for a diagnosis of PTSD. Some survivors, however, may have had a fluctuating state of consciousness and therefore may have had some experience of the event.

Some symptoms of a concussive head injury and of PTSD overlap, and where there is amnesia for the event associated with a head injury, it is important to determine, from ambulance and casualty records, the level of consciousness and whether or not this fluctuated. In the ambulance officer's and casualty reports of two such cases I have recently seen (one eighteen months and one three-and-a-half years following very serious road traffic accidents) there was evidence of patchy awareness of their circumstances, both at the scene of the accident and in the casualty department. In both cases there was, initially, total amnesia for the accident and a significant period of amnesia in relation to their subsequent admission to hospital. Both had shown post-concussional symptoms for some months and both were referred for psychiatric assessment in relation to an exacerbation of their physical symptoms. Since there was total amnesia for the accident, there was no 're-experiencing of the event' but otherwise both had symptoms satisfying the other criteria of a PTSD. It appeared that evidence of re-experiencing the event was limited to re-experiencing specific pain and other physical symptoms. This would have come as no surprise to Pierre Janet 100 years ago (van der Kolk *et al*, 1989) who argued that when such traumatic experience is not properly digested it can return as "fragmentary reliving of the trauma, as emotional conditions, somatic states, visual images or behavioural re-enactments" (p. 366).

Clearly such patients need a very careful evaluation. Interviewed under intravenous sodium amytal, both the patients referred to above regained some patchy memories of the experience and some of the affect experienced at the time and during their admission to hospital. In both cases there remained, on neuropsychological assessment, evidence of significant but not incapacitating cognitive deficits.

Dr Medley *et al's* current investigation of the survivors of the airliner crash may indeed help to clarify some of the many interesting issues raised by the diagnosis of PTSD.

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van der Kolk, B., Brown, P. & van der Hart, O. (1989) Pierre Janet on post traumatic stress. *Journal of Traumatic Stress*, **2**, 365–378.

Sir: Medley *et al* (*Journal*, January 1990, **156**, 134) raise the question of whether survivors who have amnesia for a traumatic event can develop PTSD. Our experience is that such survivors indeed can develop PTSD, although the presentation may be slightly altered.

Case report: A 22-year-old male soldier was travelling in a coach which was blown up. Eight other passengers were killed. He suffered a fractured mandible and a significant closed head-injury. He was unconscious for 36 hours and subsequently had a post-traumatic amnesia of 72 hours and a retrograde amnesia of eight hours. He made a full recovery physically from his injuries, but developed PTSD as defined by DSM–III–R within three weeks of the incident. In particular he experienced intense psychological distress and physiological reactivity on seeing a coach, with marked phobic avoidance. However, intrusive recollections did not occur and although he awoke with bad dreams he was unable to remember the content. He was treated using a cognitive-behavioural approach including *in-vivo* exposure to coaches. His symptoms improved considerably over a six month period and at the end of treatment he was able to travel by coach with only moderate anxiety.

Despite a total amnesia for the traumatic event this patient developed a significant PTSD. The lack of intrusive recollections, flashbacks or dreams is presumably related to the absence of any accessible memory. Psychogenic amnesia is a recognised feature of PTSD which could be a source of confusion, although the consistency and pattern of amnesia in this case is highly suggestive of an organic cause. It is uncertain whether the symptoms relating to coaches were as a result of being told afterwards of the event or because of a memory of it which he was not able to retrieve consciously. This man knew what had happened to him because there was much media attention and other survivors to talk to. It would be interesting to speculate how the presentation might differ in cases where such information were not available to survivors with amnesia.

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A HUNDRED YEARS AGO

An out-patient department at the Wakefield Asylum

An important movement has been made by the West Riding Council in the initiation of a scheme for the treatment of out-patients, warmly advocated by Colonel Spencer Stanhope, and now fairly established at Wakefield Asylum. The Committee, with the sanction of the General Asylums Committee, have formulated a scheme for the treatment of outdoor patients in connection with the asylum, and have passed the following resolutions with respect thereto:

1. That with a view to meeting the difficulty at present existing, and widely recognised in the early detection and treatment of mental diseases and kindred nervous affections, and in consideration of the fact that the special knowledge requisite and the appliances necessary for treatment in this branch of medicine can only be obtained, in a large proportion of cases, in asylums for the insane, the committee approve the arrangements being made at the West Riding Asylum, Wakefield, to afford an opportunity of consultation, free of charge, to those suffering from such ailments, especially in their incipient stage.
2. That the arrangements to be made be such as not to interfere with the ordinary duties of the staff, nor to cause any expense to the institution.
3. That in cases, where the Medical Superintendent thinks it desirable, the necessary medicines be supplied from the asylum dispensary at cost price, to be paid for on their delivery.
4. That no one shall be deemed to be eligible for such consultation or treatment except persons whose symptoms are, in the opinion of the Medical Superintendent, of such a nature as to require advice and treatment of the special character available at the asylum.
5. That persons desirous of availing themselves of such consultation must procure a recommendation in the prescribed form from a registered medical practitioner, or from a Justice of the Peace for the West Riding, or any county borough therein, or from the Chairman of a Board of Guardians, or from a member of the West Riding Asylums committee, and must attend at the waiting room, at the Wakefield Asylum, at the time fixed by the Medical Superintendent.
6. That it be an instruction to the Medical Superintendent to exercise due discrimination with respect to the cases to be dealt with, so as to prevent the above arrangement from interfering with the practice of the medical men in the West Riding, or in any way bringing the asylum authorities into conflict with them.
7. That steps be taken to inform the medical faculty, Guardians of the Poor of those unions whose patients are sent to the Wakefield Asylum, and the public generally of the nature of the arrangements provided under the foregoing resolutions.

That this experiment will be watched with considerable interest there can be no doubt. If it be found possible thus to encourage the friends of patients to bring the sufferers for skilled advice before the need for asylum treatment is obvious to all, and if confidence, inducing relatives to retain the care of suitable cases, can be thus engendered, something will have been done towards preventing insanity and more towards lessening the overcrowding of the asylums.

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Journal of Mental Science, 1890, **36**, 524–530.

Researched by Henry Rollin, Emeritus Consultant Psychiatrist, Horton Hospital, Surrey

British Journal of Psychiatry (1990), **156,** 913–916

Reading About . . .

Organic Psychiatry

Much contemporary psychiatry has a physical conceptualisation of mental disorders, but the term 'organic psychiatry' has a narrower meaning. Lishman (1987) defined it as the "cognitive, behavioural and emotional consequences of cerebral disorder", and distinguished it from neuropsychiatry (disorders associated with structural brain disease) and from biological psychiatry (a general approach to psychiatry). The separation of organic psychiatry and neuropsychiatry is not clear-cut, however. Presumably, delirious states lie within organic psychiatry not neuropsychiatry, even though they may result from brain disease, but tic disorders are generally considered under neuropsychiatry, even though there is no identified structural lesion.

Two other terms also merit consideration: behavioural neurology and neuropsychology. Behavioural neurology, "the study of disorders of mood, personality, intelligence, perception and arousal and . . . the structural basis of normal and abnormal behaviour" (Lees, 1988), seems to have undergone a change of emphasis recently. Possibly the first text entitled *Behavioural Neurology* (Pincus & Tucker, 1974) discussed both neurological aspects of psychiatric disorders (schizophrenia, depression) and various neurological topics from the perspective of behaviour and treatment. Latterly though, behavioural neurology has shifted its emphasis from functional psychoses to established brain disease (Kirshner, 1986), and has focused on disturbances of higher cortical function (aphasia, agnosia, apraxia, etc.), rather than abnormal emotion, personality, thought and conduct. In practice therefore, the ideal as defined by Lees (1988) is rarely attained, which is disappointing. For example, Weintraub & Mesulam (1985), discussing mental state examination, devoted only one of over 50 pages to the assessment of mood and ignored personality altogether. Kirshner's (1986) 'practical approach' offered no advice on management of emotional disorders.

Neuropsychology, "the study of neural mechanisms underlying human behaviour" (Hecaen & Albert, 1978), suffered during the early 20th century, owing to the influence of holistic and gestalt theories of brain function. However, it has flourished over the last 20–30 years. Initially, it concentrated on identifying and localising brain–behaviour relationships, aiming to elucidate normal psychological functioning and develop clinical means of localising lesions. However, the extent to which abnormal function reflects normal processing remains controversial (Shallice, 1988), and the lesion-locating power of psychological testing is far inferior to that of modern brain imaging techniques, so the emphasis has changed. Authors have adopted more clinical, less theoretical stances, and have highlighted practical aspects of clinical assessment (Lezak, 1983). A further recent shift is towards measuring recovery, planning rehabilitation and evaluating treatments (Miller, 1984). From an early focus on language and memory disorders, the range of functions studied has also widened to include, for example, attention and visual perceptual disorders (Meier *et al*, 1987).

Technological advance v. conceptual stasis

Organic psychiatry has exploited the current technological explosion in neurosciences in, for example, its use of brain imaging and molecular genetics. Brain imaging is of particular importance, useful reviews being provided by Besson (1987) and Andreasen (1988). In contrast, conceptual issues, such as debates regarding organic or psychological causation of psychopathology, or questions about localisation of lesions and functions, have advanced less far, often remaining rooted in the 19th century (Berrios & Dening, 1989). Harrington (1987) illustrated the antiquity of many current ideas on cerebral laterality (Springer & Deutsch, 1989). Morsier (1938) discussed several hypotheses of the genesis of hallucinations before opting for a very organic view. Review of the conceptual framework should stimulate fresh avenues of research (Berrios & Dening, 1989). A commemorative examination of the work of Hughlings Jackson (Kennard & Swash, 1989) is thus welcome.

Dementia

Currently, dementia is studied separately from other disorders of old age, but this was not always so. Roth

(1955) most convincingly demonstrated the varying prognoses of depression, paranoia, delirium and dementia. A more lingering issue is whether dementia is qualitatively abnormal (a disease), or simply severe but normal ageing (an idea based on continuous distributions of plaque counts or test scores (Brayne & Calloway, 1988)). However, consideration of other clinical features and family histories strongly favours the former view.

In Alzheimer's disease, the most important clinical problem is identification of early cases, since otherwise potential treatments cannot be evaluated (Henderson & Huppert, 1984). One approach, as employed by Roth *et al* (1986) using CAMDEX, is to seek subtle cognitive impairments. However, it is possible that the earliest manifestations are not cognitive but occur in other modalities of behaviour or emotion. Berrios (1989) has referred to the contemporary view of dementia as the 'cognitive paradigm', and demonstrated that earlier concepts of dementia were more broadly based than current diagnostic criteria. Non-cognitive symptoms in dementia, affective changes, behavioural problems, delusions and hallucinations, are now receiving more attention (Fairburn & Hope, 1988; Wragg & Jeste, 1989). These symptoms have most impact on where and how sufferers are cared for, so this trend is both sensible and welcome.

At the molecular level it appears that Alzheimer's disease is largely inherited (Whalley, 1989), although the aluminium story is not yet finished and seems popular with the public. The so-called transmissible dementias (Creutzfeld–Jakob disease, scrapie, etc.) have stimulated advances in microbiology such as the postulation of 'prions' (Prusiner, 1982), but with limited impact on psychiatry so far.

Movement disorders

Disorders of movement are central to organic psychiatry. Although Wernicke regarded them as organic, there has been a tendency to interpret abnormal movements psychologically, reflected in the unhelpful psychiatric classification of mannerisms and stereotypes on the basis of their being or not being goal directed. There is much interest in movement disorders in psychiatric illness (Hunter & Macalpine, 1974; Rogers, 1985) and following psychiatric treatment (Barnes, 1987). It has been suggested that schizophrenia can be regarded as a movement disorder (Barnes & Liddle, 1985).

Tics and dystonic disorders, formerly fertile ground for psychoanalytical speculations, have attracted recent interest (Lees, 1985), and Marsden has been highly influential (Marsden & Fahn, 1982, 1987; see also *Journal of Neurology, Neurosurgery and Psychiatry* special suppl., June 1989). Gilles de la Tourette syndrome forms the end of a continuum of inherited tic disorders, and is associated with obsessive–compulsive disorders (Robertson, 1989). Dystonic disorders (blepharospasm, Meige syndrome, spasmodic torticollis, writer's cramp, etc.) have an organic basis, combining genetic predisposition and a peripheral problem, for example trauma or overuse.

In Parkinson's disease (PD), improved methodology has produced some consensus about the extent of depression and cognitive impairment, although the meaning of James Parkinson's (1817) comment that "the senses and intellect appear unimpaired" still arouses controversy. Opinions differ regarding the nature and origin of depressive symptoms, or the putative link with Alzheimer's disease. Recently, a more neuropathological definition of PD has been advocated, with a fundamental role for the Lewy body (Gibb, 1989). This seems arbitrary, since clinical criteria could be used. The effect is to make the mental changes appear marginal phenomena, hampering research into psychopathology. Historically, neurologists have frequently attempted to belittle the importance of mental symptoms (for example, Brain (1930) and multiple sclerosis; Kinnier Wilson (1940) and Wilson's disease; Marsden (1982) and basal ganglia functioning). A thorough review of mental changes associated with PD is needed, taking into account the conceptual history of different viewpoints.

In the field of Huntington's disease, research into related psychopathology has been overshadowed by technical breakthroughs (Stober *et al*, 1988), especially the discovery of a marker on chromosome 4, but also neurochemical studies implicating excitatory transmitters. McHugh & Folstein (1982) and Caine & Shoulson (1983) have described the psychopathology, however, and the study of Dewhurst *et al.* (1970) is still worthwhile. Recent studies have shown psychological deficits in pre-symptomatic individuals (Jason *et al*, 1988), and associations between caudate lesions and specific cognitive deficits (Starkstein *et al*, 1988).

Wilson's disease is treatable, and produces most damage to the putamen, in contrast to other basal ganglia disorders. It is thus important, despite its infrequency. An increased prevalence of schizophrenia-like states (Davison & Bagley, 1969) and existence of a typical subcortical dementia (Cummings, 1985) have been claimed, but neither assertion is supported by recent systematic studies (Dening & Berrios, 1989*a–d*; Lang, 1989). The typical psychiatric changes are alterations in behaviour and personality, associated with dystonia and dysarthria, and probably have an organic origin.

Psychiatric trainees

Several books discuss general aspects of organic psychiatry. Lishman (1987) is indispensible. Trimble's *Neuropsychiatry* (1981), a shorter alternative, needs a new edition. Roberts (1984) uses clinical vignettes to discuss neuropsychiatric differential diagnosis. The two volumes edited by Benson & Blumer (1975, 1982) are readable, although not comprehensive. The overlap between neurology and psychiatry is considered under the editorship of Reynolds & Trimble (1989).

Among books on neuropsychology, the best general edition is by Walsh (1987). Although this is an introductory text, it has some sophisticated discussions, for example regarding frontal lobe function. A companion volume (Walsh, 1985) considers assessment, as do Strub & Black (1985). Mayes (1988) has published a useful book on memory disorders, with Parkin (1987) a less weighty alternative. Benson's *Aphasia, Alexia and Agraphia* (1979) is a classic text.

There are several helpful books on dementia (e.g. Pitt, 1987), but few on the psychiatry of movement disorders. Epilepsy is served by several volumes edited by Trimble and colleagues (e.g. Reynolds & Trimble, 1981; Trimble & Bolwig, 1986).

For lighter reading, Critchley & Henson's (1977) *Music and the Brain* is recommended. Two neurologists, Sacks (1985) and Klawans (1989), have published collections of clinical vignettes, many within the domain of organic psychiatry.

A testament to current interest in organic psychiatry has been the launch in the last year of a new journal, *Behavioural Neurology*, and two new learnèd bodies, the British Neuropsychological Society and the British Neuropsychiatry Association. Psychiatric trainees should consider joining the latter.

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British Journal of Psychiatry (1990), **156**, 917–923

Book Reviews

Editor: Sidney Crown

Anxiety: New Findings for the Clinician. Edited by Peter Roy-Byrne. Washington: American Psychiatric Press. 1989. 204 pp. £20.00.

This small volume forms part of a series entitled *Clinical Practice* and is aimed at "the clinician working outside of a hospital setting". It is based on a symposium on anxiety convened by Roy-Byrne in Washington (March, 1987). Topics covered include some of the major psychosomatic complaints related to anxiety (pseudo-angina, hyperventilation and irritable bowel syndrome), the relationship between alcohol abuse and anxiety, cardiac neurosis, and overviews of the pharmacological and behavioural strategies available for anxiety management, as well as a chapter on caffeinism. The book's orientation is heavily biological, with an emphasis on the noradrenergic overactivity theory of anxiety and on antidepressants as treatment of first choice. Clinical descriptions, based mainly on one or two detailed case descriptions per chapter, are clear and helpful. Each chapter is well referenced up to 1987, and the DSM–III–R classification is adhered to throughout.

The 'office-based' private psychiatrist without links to a hospital or an academic department is, for the time being, unusual in this country. The British market for this book is therefore likely to consist mainly of trainees, for whom it offers a reasonably cheap and up-to-date, although biologically-biased, review of the aetiology and management of anxiety disorders. If the Government's plans for the National Health Service (NHS) are fulfilled however, the British market for the second edition of this book may expand considerably.

Cornelius Katona, *Senior Lecturer in Psychiatry, University College and Middlesex School of Medicine*

Advances in Test Anxiety Research, vol. 6. Edited by R. Schwarzer, H. M. van der Ploeg and C. D. Spielberger. Netherlands: Swets & Zeitlinger. 1989. 320 pp. DGl 59.50 (pb).

This latest collection of conference papers and invited chapters should be read by anyone who wishes to know the latest details of the interactions between anxiety and performance on tests of mental ability. None of the chapters claim any direct psychiatric or clinical relevance, but several will appeal to those with a general interest in anxiety.

The book is divided into four sections. The first comprises five papers which focus upon the relationship between anxiety and cognition. For example, that by Boggiano *et al* reveals a link between extrinsic motivation and variables such as helplessness and large performance decrements following negative feedback. In addition, Rost & Schermer provide a useful new model of test anxiety which will surely generate considerable research and may be generalised to other forms of anxiety.

In the second section linking test anxiety to specific behaviour, Kalechstein *et al* reveal that procrastination is a distinct construct from test anxiety, although it is associated with tension, worry and irrelevant thinking. Unfortunately though they do not ask *why* so many of us choose to perform in such a way. Those with a morbid fear of statistics may find comfort in the chapter by Benson & Bandalos who show that statistical text anxiety can be differentiated from general test anxiety. Numbers *do* hold a unique horror.

Although the final two methodological and cross-cultural sections comprise more than half the book, only one paper – that by Rost & Schermer – is likely to interest Journal readers. This examines strategies used to cope with anxiety, and finds four exceptionally clear-cut factors which may well have more general applications in anxiety research. The remainder may be invaluable to those who measure test anxiety worldwide, but are of little general interest.

This is not a book for the complete novice, nor for someone who simply wants a brief overview of this important field. However, it is an invaluable source of information and ideas for the specialist or anyone with a general interest in the anxiety construct. The papers have been well-edited and generally seem to be methodologically sound, although the lack of a subject or author index is a constant irritant.

Colin Cooper, *Department of Psychology, University of Ulster*

Depression: Recognition and Treatment in General Practice. By D. G. Wilkinson. Oxford: Radcliffe Medical Press. 1989. 95 pp. £8.50.

It is important that general practitioners (GPs) recognise and manage depression because it is common and the associated morbidity can be significant. Nearly 13%

of consecutive adult attenders presenting a new problem to a GP suffer from major depressive disorder (DSM–III–R).

This book for GPs on recognition and treatment of depression is a modification of a previous guide for lay people and therein lie its advantages and disadvantages.

The main advantage is the easy-to-read style. It can be read within a couple of hours and is therefore useful to medical students and GP or psychiatry trainees revising for exams. GPs will find the final section particularly helpful as it is devoted to self-help for sufferers and their helpers. The author expressly permits the GP to make copies for patients.

The main disadvantage is that the book retains its simplistic approach and omits many recent findings. The section on recognition of depression occupied only one-sixth of the book. Tables are not always referenced or explained. A table entitled "the cues for the recognition of depression" appeared to be adapted from Burton & Freeling's paper. It was not explained that this table largely represented the cues thought likely to be important by a GP audit group. When the same GPs tested these cues they found that one of them did not happen and the others did with varying frequency. Important findings by Freeling *et al* and Sireling *et al* about the recognition of depression, well known to GPs, are not discussed. Similarly, in the treatment section recent evidence by Hollyman *et al* for the value of amitriptyline in major depression in general practice is omitted, yet is well known to many GPs. The newer available antidepressants that work on 5-hydroxytriptamine (5-HT) as well as others in the pipeline are omitted.

I must conclude that this book has not successfully achieved its intended metamorphosis into an up-to-date resource for GPs, but it does contain much useful information.

ANDRÉ TYLEE, *Senior Lecturer in General Practice, St George's Medical School*

Autism: Explaining the Enigma. By UTA FRITH. Oxford: Basil Blackwell. 1989. 204 pp. £8.95 (pb), £25.00 (hb).

I cannot remember when I last enjoyed reading a book for review so much. This is a little gem, worth every penny of the cost, particularly at the paperback price.

There is a large and often confusing literature available about this rare and mysterious condition, but this book goes a long way towards realising its subtitle – *Explaining the Enigma.* In eleven clear chapters, Frith sets out the classic clinical picture, the historical and literary perspectives, the epidemiology and the biological origins of autism. Then, via the chapter on intelligence test findings, she moves on to hypothesise about the precise cognitive deficit underlying the disorder and concludes that there is a lack of, or 'weak drive towards' central coherence in cognitive function. The normal perceptual abilities of autistic people have been demonstrated by many others, including Lorna Wing, who herself postulated a deficit in the central processing of information. Frith examines this hypothesis more closely and goes on to explore the links between it and the observed abnormalities in communication, relationships and behaviours of autistic individuals. A crucial consequence of the dysfunction in central coherence is that autistics lack a theory of mind, either as applied to themselves or to others; they lack the ability to 'mentalise'. Put another way, they do not know that they (and others) know.

Treatment of autism is only mentioned as a small section of the final chapter, and the author makes no apology for this. As she puts it: there is no getting around the fact that so far the underlying condition has been untreatable. However, she makes a consistent plea for a deeper and more widespread understanding of the core deficit as the basis for more successful management of the autistic individual.

The book is thoroughly researched with a separate and extensive bibliography for each chapter. The author's influences, including mentors and co-researchers are familiar names in the field of autism research worldwide. The style is clear, logical and, above all immensely readable, amply illustrated by case vignettes and drawings, including occasional amusing cartoons.

The book could be read by any professional, even probably by any interested lay-person, particularly if he or she enjoys following a logical, deductive narrative.

PATRICIA AINSWORTH, *Lecturer in Child and Adolescent Psychiatry, University of Manchester*

Autism: Nature, Depression and Treatment. Edited by G. DAWSON. New York: The Guilford Press. 1989. 417 pp. $45.00.

This is an intense book: it stands out from other recent books on autism (by Schreubiner and Shopler & Mesibov) because of its tackling of cognitive-linguistic and neurobiological issues in considerable depth. The six chapters on linguistic, neuroanatomical, neurochemical, genetic and processing perspectives require some sound basic knowledge of the subject and are highly complex although fascinating. Indeed, for someone not in these specialities, as much knowledge is gained about these subjects as about autism and its possible neurobiological causes. Some chapters I found frankly incomprehensible, for example, that on the interface between sensory and information processing (Ornitz). There seemed to me to be too much on attentional and neurophysiological aspects which as yet are not considered to be central to the defects or aetiology. This bias is perhaps accounted for by the editor's area of interest.

This is generally not a clinical book. There is so little on clinical features, diagnosis or classification that one has to take it on faith that we all understand what is meant by autism. I found the book the slighter for not having addressed certain phenomenological conundrums and for being so wholly theoretical (with the exception of the treatment chapters).

This is a high-powered, tightly-packed book of academic considerations with no light relief expected or given. The non-personness of autism is well illustrated by the non-personness of this book, with no mention of individuality. The book mainly raises awareness of possible theories to explain autism, brings us knowledge of recent research, but provides no definitive answers. The chapters on new directions in diagnosis and treatment largely develop theoretical issues and do little to clarify efficacious treatment approaches.

For those specialising in this field this is an important book with in-depth insights into many possible mechanisms. For the rest of us child psychiatrists, those with an interest in autism will find some chapters bringing in new ideas such as that by Hobson on "Beyond cognition" and Flinsberg on "The psycholinguistic perspective". The introduction to the book is also excellent. We should spare ourselves struggling with this book as a whole but dip into it to explore areas that whet our appetites.

CLAIRE STURGE, *Consultant Child Psychiatrist, Northwick Park Hospital, Harrow*

Panic Disorder: Theory, Research and Therapy. Edited by ROGER BAKER. Chichester: John Wiley & Sons. 1989. 350 pp. £37.00.

This compilation of essays from around the globe deals with an old disorder, anxiety, under a new name: panic. Proposed by Spitzer in 1975, panic disorder entered the DSM–III in 1980, and ever since, grave doubts have been cast on its existence by, for example, Gelder. The book has a case to prove, but the high quality research it contains provides more evidence against the disorder than for it. For instance, the opening chapter describes the enormous number of precipitants to panic disorder and the sheer variety of clinical settings in which it can occur, suggesting a final common pathway rather than a discrete disorder.

Despite a plethora of physiological studies, no consistent biological marker for the disorder has emerged. Freedman reports that naturalistic monitoring studies have consistently found no basal differences between sufferers and controls on any measure. Only in the laboratory do differences emerge. Perhaps the controls who volunteer for such experiments involving laboratory-induced panic cannot be considered normal, at least in the lay sense of the term.

In an illuminating chapter, Baker classifies the mechanisms by which personal accounts contribute to scientific development. We learn that long before cognitive and behavioural methods of treatment were known to psychiatrists, individual sufferers had discovered these techniques for themselves. An epidemiological study by von Korff & Eaton finds a long latency period between sufferers first experiencing panic attacks and developing panic disorder. They express the hope that one day this may justify a massive public health programme to prevent the disorder. The more critical approach adopted by Hallam and then Marks, produce two of the best chapters in the book: provocative and well focused.

Overall, however, there is a surprising neglect of such issues as the bedroom, the family, the workplace and the Social Security Office in relation to panic disorder. A chapter on the contextual approach to panic raised my hopes but the context is the consulting room.

There is a comprehensive but uninspired literature review on aetiology, followed by a section on treatment. Five chapters full of handy tips from experienced practitioners form an invaluable guide for those who work in out-patient clinics.

By the end I had come to agree with the editor's remarks in the preface about the seminal role of the DSM–III in stimulating research. The best contributions were from those workers whose research was provoked by a lack of agreement between its 'diagnostic precision' and their own clinical intuitions – rather in the way that the work of Freud, Beck and Marks was a reaction to the prevailing orthodoxies of the day.

PAUL WOLFSON, *Senior Registrar in Psychiatry, St Thomas' Hospital, London*

Sexual Desire Disorders. Edited by SANDRA R. LEIBLUM and RAYMOND C. ROSEN. New York: Guilford Publications. 1988. 470 pp. £26.95.

While excessive sexual desire is touched upon in this substantial book, it primarily addresses the problems of low or absent sexual desire. This is the most prevalent sexual dysfunction among women in the general population and those presenting for help at sexual dysfunction clinics. Interestingly, while men with low sexual desire are seen only occasionally in sexual dysfunction clinics in the UK, the situation is very different in the USA, where almost as many men as women seek help. Compared with the results of sex therapy for most other sexual dysfunctions, desire problems often have a poor outcome, especially in the long term. Low sexual desire therefore presents a commonly encountered challenge to current therapeutic approaches and the Editors are to be congratulated on putting together a timely work on this important topic. The book is considerably enhanced by case examples chosen to demonstrate both positive and negative therapeutic outcomes, which provide useful perspectives on treatment.

The initial chapter by the Editors provides an excellent introduction to the problem of low sexual desire, highlighting major issues such as: what is sexual desire; can it be measured; and are there gender differences in desire? There follow three chapters dealing with psychodynamic and interpersonal perspectives on sexual desire. I found the second section of the book, which includes four chapters on cognitive and behavioural aspects of sexual desire problems, the most helpful in terms of providing ideas for improving therapeutic approaches.

The broad-spectrum treatment approach described by LoPiccolo & Freidman emphasises the need for therapists to be flexible in planning treatment in the light of the many issues which can underly disorders of sexual desire. The chapter by Lazarus on multimodal perspectives includes a useful mnemonic (BASIC ID) for remembering the areas to which assessment and therapy may need to be directed – behaviour, affect, sensation, imagery, cognition, interpersonal relationships and drugs (biological factors). The Editors then contribute an interesting account of a sexual scripting approach. Sexual scripts refer to the cognitive framework which guides a person's sexual behaviour and which usually has a firm basis in the individual's sexual background and attitudes common to the person's gender. The chapter by Zilbergeld & Crammond on the use of hypnosis for treatment is fascinating and yet, at the same time, so 'Californian' in approach that the therapeutic strategies would be difficult to translate into clinical practice in the UK.

The third section of the book on systems and interactional perspectives on low sexual desire includes two chapters. The first, an account of the approach used in the Masters & Johnson Institute, is disappointing because little progress appears to have been made there beyond the acceptance that, unlike in Masters & Johnson's original formulation, low sexual desire exists as a discreet dysfunction. The other chapter, by Verhulst & Heiman, describes a useful systems therapeutic approach in which interactions between partners are grouped into three categories – sensory, affective and symbolic. Therapy is directed at whichever level of interaction appears to be maladaptive. One interesting therapeutic approach used by the authors is very brief individual psychotherapy of one partner with the other partner present.

The fourth section of the book addresses biological and medical aspects of sexual desire problems. There are two splendid chapters by Seagraves. The first is a thorough review of the evidence concerning the relationship between libido and hormones in both sexes – I would recommend this to anyone wishing to obtain an overview of this topic. The second is an equally impressive account of the effects that medication and substances of abuse can have on sexual desire. The third chapter in this section, which considers desire problems that may occur in the physically disabled, would have benefited from the inclusion of guidelines for therapists.

The final section begins with an insightful chapter concerning sexual desire problems in lesbian couples. The low frequency of sexual activity in many such couples raises the question of whether desire problems in heterosexual couples are defined largely from the perspective of male levels of desire rather than those intrinsic to many females. The second chapter in this section is an sensitive account by Coleman & Reece of desire disorders in gay men.

This outstanding book is essential reading for all workers in this field who wish to get a thorough grasp of the complexities of sexual desire disorders and their treatment. Hospital libraries should certainly have a copy.

KEITH HAWTON, *University Department of Psychiatry and Warneford Hospital, Oxford*

Male Homosexuality: A Contemporary Psychoanalytic Perspective. By RICHARD C. FRIEDMAN. London: Yale University Press. 1988. 296 pp. £27.50/$42.50.

This book tackles a difficult and sensitive subject well. I would strongly recommend it to all psychiatrists. The main question addressed is that of integrating the concept of homosexuality as a pathological entity with it as an expression of normal human sexuality. It is difficult to know how successful this attempt has been.

A review of the biological aspects of sexuality is followed by a discussion of sociological research. This includes a review of the Kinsey investigations. Different psychodynamic models are then examined. The author struggles unsuccessfully to reconcile a model of homosexuality as being on the same level as heterosexuality, while at the same time holding on to Freud's psychodynamic models. One problem is to know how to deal with oedipal anxieties using this approach. It also blurs the issue of the child having to deal with the capacity of heterosexual relationships to produce children and all that this implies for the individual and his relationship with his parents. However, the author goes on to demonstrate a useful approach using self psychology. Helping the client to integrate their sexuality into the rest of their concept of self can have a strong healing effect. It is pointed out that there is a need to distinguish homosexuality from underlying psychopathology. There is a tendency, because of attitudes in our culture, to ascribe say borderline psychopathology to associated homosexuality, when to do the same thing with heterosexual orientation would not seem relevant. At the same time it is pointed out that various aspects of 'homosexual' behaviour can be pathological – such as the lack of object relatedness in promiscuity. However, again, this is no different from similar aspects of heterosexual behaviour.

A three-dimensional classification system is suggested which I found too complex. Although the author is clearly very committed to diagnostic systems, in many ways the message of this book is that there is no such thing as a homosexual, just people whose sexual orientation happens to be homosexual.

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New Essays on Narcissism. By Bela Grunberger. Translated and edited by David Macey. London: Free Association Press. 1989. 205 pp. £27.50 (hb).

Narcissism has been recognised by medics for many years. Freud considered that the infant was self-engrossed, an alimentary canal to be fed at one end and cleaned at the other, demanding immediate attention to its needs, libido being attached to itself. As the child matures it removes some of this libido from itself and attaches it to the mother. During bereavement libido is withdrawn onto or into the self once more.

There is an element of self-love or self-esteem in the healthy adult, which is necessary for the maintenance of a feeling of well-being. Schizophrenics are said to have an excess of narcissism, having withdrawn libido from a hostile environment. Freud himself noted this. Narcissistic personality disorder is uncommon in ordinary psychiatric practice. Such personalities are somewhat less prone to psychotic decompensation than are borderlines. Hysterical personality disorder can also be distinguished from narcissistic personality disorder.

Some orthodox psychiatrists would suggest that a so-called Barnum effect (after the circus owner) is operative in describing personality disorders in general and narcissistic personality disorder in particular: we are inclined to overgeneralise when describing people. Psychoanalytic formulations in this area are derived from a handful of cases. It has also been argued that the criteria for diagnosing excessive narcissistic traits come uncomfortably close to the selection criteria for analysis. These considerations have not however stemmed the tide of publications on this subject by such as Kohut, Kernberg and Grunberger.

Grunberger speaks of a 'monad' which is the intangible protective swaddling provided by the womb during pre-natal life and the caring mother after birth. The latter should normally also promote gradual individuation. The drives take over, the Oedipus complex is negotiated and a mature adult emerges. Grunberger discusses the legacies of Narcissus and Oedipus in relation to the client, the analyst, anti-Semitism, and fetishism (orthodox psychiatrists would draw firmer boundaries between narcissism and fetishism than Grunberger does).

Grunberger is a Hungarian working in France. The style of the book is somewhat turgid. This may in part be related to the problem of translation. However, psychoanalysts would do well to order their thinking and not to try to say too much in long, Latin sentences. This heavy style puts the book beyond the patience of most readers.

Brian O'Shea, *Consultant Psychiatrist,*
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Life Events and Illness. Edited by G. W. Brown and T. O. Harris. London: Unwin Hyman. 1985. £35.

George Brown and his colleagues have been beavering away for half a lifetime on the subject of the social origins of illness. Their work has involved creating an instrument worthy of the subjects it is investigating. Some would say it is the only one that does justice to the complexity of human thought and feeling as well as behaviour. The early psychologists despaired of this task and landed us with the often simplistic behaviour checklists so beloved of learning theorists. The psychoanalysts largely refused to try to measure, claiming that every human dilemma was unique so that categorisation was invidious and useless. What Brown & Harris did, however, was to make it possible once more for the *meaning* that the individual attributes to an event to be measured and evaluated.

Having demonstrated the value of the Life Events and Difficulties Schedule (LEDS) for understanding the social origins of depressive illness, its originators have now trained a number of enthusiastic followers who have applied their methods to a variety of physical and psychiatric illnesses: anxiety, schizophrenia, depression, appendicectomy, abdominal pain, menstrual disorders, multiple sclerosis, myocardial infarction and dysphonia – uncomfortable bedfellows one might think, and certainly the results are a motley collection.

Depression appears to be associated with the experience of *loss* (this need not be a physical loss but may involve loss of meaning, loss of esteem, etc), while anxiety seems to follow from a *threat of danger*. Finlay-Jones's study of women in a general practice in London, reported here, found that parental divorce in childhood was significantly associated with the onset of anxiety among women, but only those who had also experienced a recent severe danger.

The experience of intrusiveness seems to precede the onset of schizophrenia in vulnerable individuals. Calloway & Doran use the LEDS inventory to explore endocrine changes in depression, and have fascinating things to say about the effect of life events on the immune system. Their work in an appropriate bridge to the next section of the book which deals with physical illness and adversity.

Here, the evidence for straight-forward associations is less clear. Creed's much quoted work, for example, is not convincing in those cases where there was inflammation of the appendix, although the lily-white ones did seem to be related to preceding adversities. The associations between adversity and multiple sclerosis, menorrhagia and myocardial infarction are only convincing if a longer period of time is examined for adverse life-events. Moreover, there are other studies of adversity and the onset of physical illness which are not looked at in this section – diabetes, accidents, alcoholism, impotence, and breast cancer for example as well as self-poisoning, shoplifting and unemployment.

The chief value of the book for me was the detail with which the editors examine the use of the LEDS and its application to other cultures and situations. It seems to me a very flexible and scientifically-useful tool with which to take psychiatric research into the 21st century. It is sociologists who have at last found a way of uniting the in-depth psychology of Freud and his followers with the measurers. This volume is essential reading for all psychiatrists and should be found in all post-graduate psychiatric libraries.

DORA BLACK, *Consultant Child Psychiatrist, Royal Free Hospital, London*

Ethnic Factors in Health and Disease. Edited by J. K. CRUICKSHANK and D. G. BEEVERS. London: Wright. 1989. 324 pp. £39.50.

The rather general title is a misnomer, for this reference volume is concerned essentially with the epidemiology of *minority* ethnic groups in Britain and of those New Commonwealth countries from which Black immigrants to Britain have come. 'Ethnic factors' among White Europeans are barely considered for they serve here as the standard reference group, one itself without ethnicity, without culture; there is no consideration either of the wider European or Third World context, or indeed of our Polish, Italian and Jewish communities, while the Irish (the largest foreign-born group in Britain) scrape a brief mention.

It is indeed difficult to determine what an 'ethnic factor' might be. The editors came down firmly in favour of the terminology of 'ethnic group' rather than that of 'race', although the latter reappears in the sociological and psychiatric sections. One author, however, still favours the old term 'Caucasian' (coined in 1795 by Johann Blumenbach because Noah's Ark landed on Mount Ararat). The general tenor of the collection might be described as liberal biomedicine, despite the unfortunate first sentence of the foreword which tells of "mankind's blackest hours".

The book certainly provides an unparalleled synopsis of current medical knowledge in its area and will become a standard reference work for physicians working in Britain particularly. Crisp summaries introduce general epidemiological methodology and population genetics, and its 41 chapters consider general mortality rates, nutrition and obesity, pregnancy, circulatory disorders, haemoglobinopathies, neoplasms, retroviruses, TB, sarcoidosis and psychoses. The emphasis is on biomedical knowledge and explanations, with brief accounts of dietary patterns and of the ethics of screening. One is struck by the difficulty faced by all the authors in integrating cultural and behavioural data into their analysis, such data serving merely as a hypothesised zone of unexplained statistical variance. Local knowledge, when considered at all, is perceived as a fit, or otherwise, with biomedicine: not surprisingly we find the old idea that prohibitions on pork are grounded in knowledge of infection despite the large body of knowledge (none cited here) on the anthropology of food.

The sociology chapter (Pearson) remains quarantined in its unique section. Together with the general psychiatric overview (Burke), it constantly points to nosocomial factors, which are affected by services and medical power – but these are ignored in the other papers. Psychiatric epidemiology is admittedly based primarily on service contact and there are few community studies on the mental health of Black and ethnic minority groups. The other psychiatric chapters also examine what one author calls 'non-artifactual differences' – those patterns located in the individual or his/her culture independent of the wider political context. All three (McGovern, Harrison, Glover) present published work on the high incidence of diagnosed schizophrenia in the children of Afro-Caribbean migrants but no new theories, apart from Glover's suggestion of a cohort effect in which people of Afro-Caribbean origin develop schizophrenia when younger, thus inflating in part the figures for the 1980s.

Genetics, selective patterns of migration and diet aside, the general medical contributions come up with few explanatory models. The editors' suggestion that readers interested in 'sociological explanations' should consult Rathwell & Phillips' *Health, Race and Ethnicity* (actually a view from medical geography) takes a rather narrow view of *illness*, one repeatedly conflated here with *disease*. Contributions on patients' own understandings of health and sickness, of how such general notions as racism and disadvantage are actually translated into personal experience or pathophysiology are sadly missed. These would be useful not just for some humanistic genuflection but because of their potential explanatory value within biomedicine. The old (and as yet unsubstantiated) notion that minorities stigmatise 'mental illness' more than the White English reappears a couple of times.

ROLAND LITTLEWOOD, *Reader in Psychiatry and Anthropology, University College, London*

Health Services Planning and Research: Contributions from Case Registers. Edited by J. B. WING. London: Gaskell. 1989. 126 pp. £7.50.

This publication is essentially a Department of Health and Social Security (DHSS) document produced on behalf of the Royal College of Psychiatrists. It is a collaborative work by the joint UK Inter-register Committee and makes available much statistical data accumulated by the nine case registers covering selected areas in Great Britain. It also attempts to derive some direction towards better planning of services.

For a short publication it contains considerable information and is at times heavy reading. A useful introduction by the editor includes an overview of the characteristics, strengths and weaknesses of case registers. Part II then describes in detail the changing trends in in-patient care between areas, and in separate chapters, utilises selected data to highlight the evolving situation within one urban area, the effects of population changes on the requirement of long-stay facilities, and difficulties arising from the planned rundown of a traditional psychiatric hospital. Part III contrasts community psychiatric nursing services in different areas, assesses the use of psychogeriatric services, and evaluates the outcome of a five-year follow-up of deliberate self-harm in two areas.

What is central to the philosophy of this authoritative publication is that information derived from case registers can be used in forward planning. In the light of the current National Health Service (NHS) White Paper, this whole subject can hardly be more topical. In the final section there is some encouragement – if limited guidance – for those wrestling with the complexities of medical audit.

Not a book for bed-time reading, more for study and reference. It represents a step forward towards matching evaluation with provision of psychiatric services.

FREDERICK A. HORROCKS, *Senior Registrar, EMI Unit, Wrexham Maelor Hospital, Wrexham, Clwyd*

Psychoactive Drugs: Tolerance and Sensitisation. Edited by A. J. GOUDIE and M. W. EMMETT-OGLESBY. USA: Humana Press Inc. 1989. 608 pp. $79.50.

This is a relatively large, up-to-date and expensive book, which is clearly presented, with simple and easy-to-read diagrams as well as clear tables. The volume commences with an overview by the editors which sets the subject matter in its historical perspective. Part I then provides four chapters reviewing behavioural mechanisms in drug tolerance and sensitisation; Part II consists of four chapters covering molecular mechanisms in the same subject; and Part III consists of two summary chapters, one concerning behavioural tolerance and sensitisation and the other providing a pharmacological overview.

The editors in their preface suggest that the text will be of value to researchers in a variety of disciplines, to post-graduates, and also in some cases to advanced under-graduate teaching. I would agree that the book would be valuable to researchers and certain post-graduate workers since it is a collection of highly specialised contributions by leading workers in their fields. It is also a book that would be of interest to pharmacologists and to some psychiatrists, but it is too specialised for a general medical readership.

ANNA HIGGITT, *Consultant Psychiatrist and Honorary Senior Lecturer, St Charles Hospital, London*

Cognitive Therapy in Practice: A Case Formulation Approach. By JACQUELINE B. PERSONS. London: W. W. Norton & Co. 1989. 242 pp. £17.50.

There has been a recent increase in the number of books published on clinical approaches to cognitive therapy on both sides of the Atlantic. However, Jacqueline Persons' book is likely to be one of the survivors in this increasingly competitive market. While it will mainly appeal to novice therapists, the more experienced workers in this field will also gain from the information presented. The author emphasises the formulation approach to cognitive therapy. This is very important as many text books neglect this aspect of the approach or indeed ignore it completely. Novice cognitive therapists are, therefore, often left with the impression that the therapy can be approached in a 'cook-book' manner where different techniques are simply pulled out at random. This book advocates the need to develop a more coherent approach to an individual's problems so that logical decisions can be made about which technique to use.

The book is well laid-out and the author's style is clear and understandable. The chapters are well thought out and I have no major criticisms to offer. Most examples of the different cognitive and behaviour techniques available focus on anxiety and depression management. The author not only outlines the interventions but also gives practical demonstrations of how to use these techniques. This is important for therapists new to the field and, although the examples are fairly straightforward, they are also clearly written. Useful additional chapters are included on dealing with suicidal patients and on ensuring that the therapist uses cognitive behavioural techniques on themselves, particularly if they are finding a client's problems difficult to overcome. My one minor complaint is that the chapter on the relationship between the cognitive therapist and the client is not put earlier in the book to emphasise that this is an important part of this type of approach. However, the chapter itself is well presented and Jacqueline Persons draws on her own research in this area as well as on clinical material to illustrate the importance of paying adequate attention to transference and counter-transference issues.

As one of the organisers of a multidisciplinary post-graduate course on cognitive therapy, I have recommended this book to our trainees to aid the development of their clinical skills.

JAN SCOTT, *Consultant and Senior Lecturer, University Department of Psychiatry, Newcastle upon Tyne*

Contents of
THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 5 **May 1990**

Special Articles

543 Cults and zealous self-help movements: a psychiatric perspective. *Marc Galanter*

552 Affective spectrum disorder: does antidepressant response identify a family of disorders with a common pathophysiology? *James I. Hudson and Harrison G. Pope, Jr*

565 Irritable bowel syndrome and psychiatric illness. *Edward A. Walker, Peter P. Roy-Byrne and Wayne J. Katon*

Regular Articles

573 Inverse relationship between defensiveness and lifetime prevalence of psychiatric disorder. *Richard D. Lane, Kathleen R. Merikangas, Gary E. Schwartz, Suzanne S. Huang and Brigitte A. Prusoff*

579 Caffeine augmentation of ECT. *C. Edward Coffey, Gary S. Figiel, Richard D. Weiner and William B. Saunders*

586 Gender weighting of *DSM-III-R* personality disorder criteria. *June Sprock, Roger K. Blashfield and Brenda Smith*

591 Oral *S*-adenosylmethionine in depression: a randomized double-blind, placebo-controlled trial. *Bruce L. Kagan, David L. Sultzer, Nicholas Rosenlicht and Robert H. Gerner*

596 Structured interview data on 102 cases of multiple personality disorder from four centers. *Colin A. Ross, Scott D. Miller, Pamela Reagor, Lynda Bjornson, George A. Fraser and Geri Anderson*

602 Suicide and schizophrenia: data from a prospective community treatment study. *Lawrence J. Cohen, Mary Ann Test and Roger L. Brown*

608 Depressive episodes and dysphoria resulting from conjugal bereavement in a prospective community sample. *Martha Livingston Bruce, Kathleen Kim, Philip J. Leaf and Selby Jacobs*

612 Mortality in a group of formerly incarcerated juvenile delinquents. *Catherine A. Yeager and Dorothy Otnow Lewis*

615 Addition of lithium carbonate to carbamazepine: hematological and thyroid effects. *Keith G. Kramlinger and Robert M. Post*

621 Response to treatment with antidepressants of patients with severe or moderate nonpsychotic depression and of patients with psychotic depression. *James H. Kocsis, Jack L. Croughan, Martin M. Katz, Thomas P. Butler, Steven Secunda, Charles L. Bowden and John M. Davis*

625 Diagnosis and clinical course of erotomanic and other delusional patients. *Marie Rudden, John Sweeney and Allen Frances*

629 Reduced dark-adaptation: an indication of lithium's neuronal action in humans. *Hinderk M. Emrich, Josef Zihl, Costas Raptis and Anna Wendl*

632 Sexual and physical abuse histories and psychiatric symptoms among male psychiatric outpatients. *Chester Swett, Jr, Janet Surrey and Caryn Cohen*

637 Major depression in patients with social phobia. *Murray B. Stein, Manuel E. Tancer, Cheryl S. Gelernter, Bernard J. Vittone and Thomas W. Uhde*

640 Impact of life events on subjects with panic disorder and on comparison subjects. *Ronald M. Rapee, Eric M. Litwin and David H. Barlow*

645 Convergent validity of measures of PTSD in Vietnam combat veterans. *Miles E. McFall, Dale E. Smith, Douglas K. Roszell, David J. Tarver and Kenneth L. Malas*

Commentary

649 Will we save the homeless mentally ill? *H. Richard Lamb*

Clinical and Research Reports

652 Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. *Christopher J. McDougle, Wayne K. Goodman, Lawrence H. Price, Pedro L. Delgado, John H. Krystal, Dennis S. Charney and George R. Heninger*

655 Lithium treatment for cocaine abusers with bipolar spectrum disorders. *Edward V. Nunes, Patrick J. McGrath, Steven Wager and Frederic M. Quitkin*

658 Patterns of depressive symptoms in expectant and new parents. *Valerie D. Raskin, Judith A. Richman and Cheryl Gaines*

661 Autoantibodies to brain lipids in schizophrenia. *Anthony L. Pelonero, Anand K. Pandurangi and Vincent P. Calabrese*

Contents of The Journal of Nervous and Mental Disease

May 1990 **Volume 178, Number 5**

Editorial. Biomedical science and the changing culture of clinical practice. *Eugene B. Brody* 279

Frontal lobe dysfunction following closed head injury. A review of the literature. *Audrey J. Mattson and Harvey S. Levin* 282

Perceptions of general and specific therapist behaviors. *Derrick Silove, Gordon Parker and Vijaya Manicavasagar* 292

Welfare status and psychosocial adjustment among 100 Hmong refugees. *Joseph Westermeyer, Allan Callies and John Neider* 300

Panic disorder without fear in patients with angiographically normal coronary arteries. *Bernard D. Beitman, Matt Kushner, Joseph W. Lamberti and Vaskar Mukerji* 307

Infrequent and limited-symptom panic attacks. *David A. Katerndahl* 313

The unipolar-bipolar distinction in the characterological mood disorders. *Daniel N. Klein, Ellen B. Taylor, Kathryn Harding and Susan Dickstein* 318

Bulimia nervosa in overweight individuals. *James E. Mitchell, Richard L. Pyle, Elke D. Eckert, Dorothy Hatsukami and Elizabeth Soll* 324

Psychiatric disorder in male veterans and nonveterans. *Grayson S. Norquist, Richard L. Hough, Jacqueline M. Golding and Javier I. Escobar* 328

Book Reviews. American Psychiatric Association Task Force on Treatments of Psychiatric Disorders. *Treatments of Psychiatric Disorders;* Warren, C. A. B. *Gender Issues in Field Research;* Tarter, R. E., Van Thiel, D. H. and Edwards, K. L. (eds) *Medical Neuropsychology: The Impact of Disease on Behavior;* Gorizontov, P. D., Belousova, O. I. and Fedotova, M. I. *Stress and the Blood System;* Mann, J. J. (ed) *Phenomenology of Depressive Illness;* Greenberg, D. F. *The Construction of Homosexuality;* Barrett, J. E. and Rose, R. M. (eds) *Mental Disorders in the Community: Findings from Psychiatric Epidemiology*

Index to Advertisers

Pharmaceuticals

The Boots Company plc	*facing* p 808
Duphar Laboratories Ltd.	*facing* p 809
Janssen Pharmaceuticals Ltd.	p vi
Janssen Pharmaceuticals Ltd.	*facing* p 827
Janssen Pharmaceuticals Ltd.	*facing* p 870
Lederle Laboratories Ltd.	*facing* p 808
Eli Lilly	*facing* p 834
Eli Lilly	*facing* p 835
Lundbeck Limited	outside back cover
Lundbeck Limited	inside front cover
E. Merck Ltd.	*facing* p 826

Appointments

Western Sydney Area Health Service	p v
Association of Commonwealth Universities	p iv

Clinics, Hospitals and Nursing Homes

St. Andrew's Hospital	*facing* p 871

Miscellaneous

Anna-Monika Foundation	*facing* p iv
London School of Economics	p iv
Wellcome Trust	p ii

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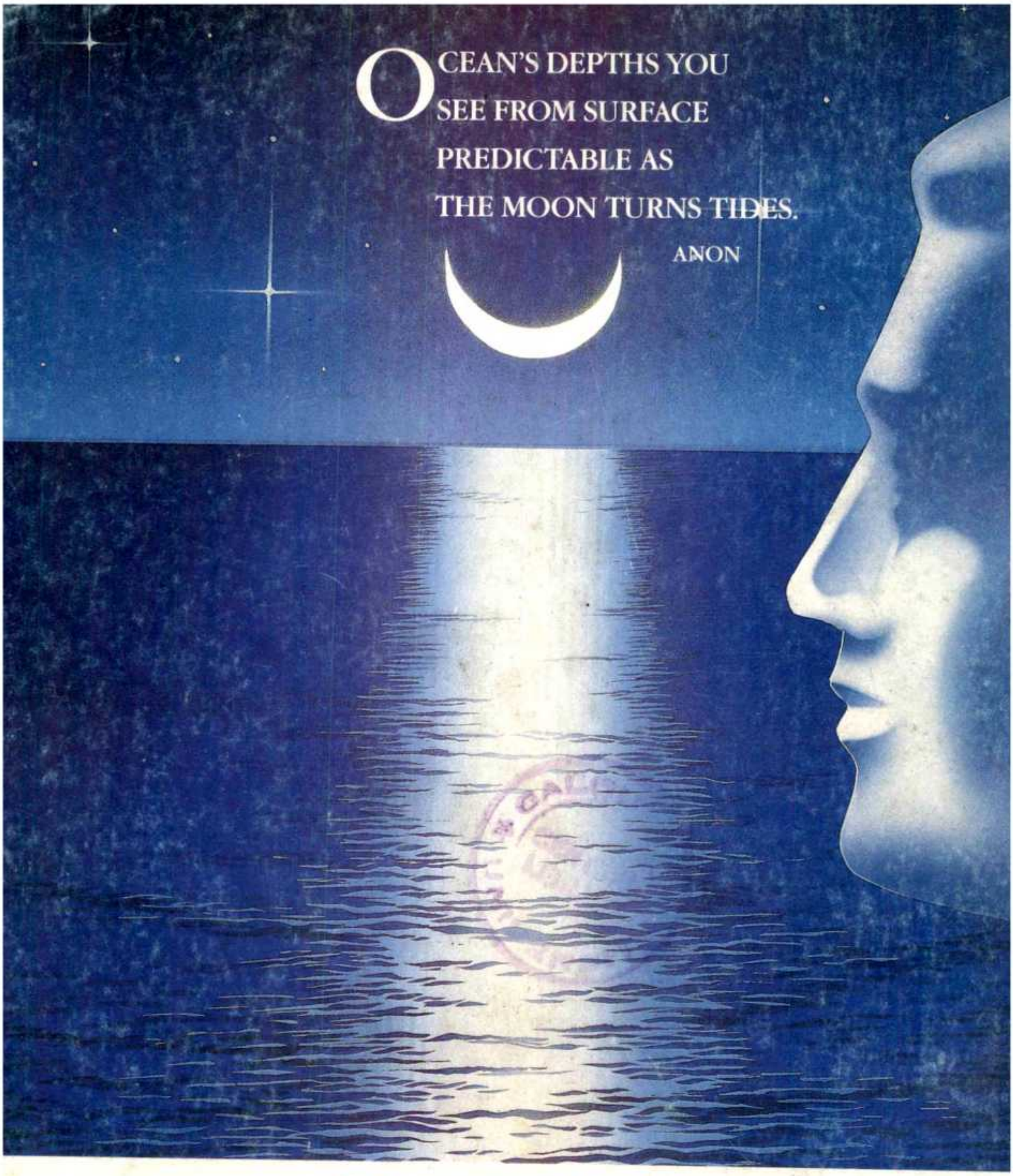

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M. T. Abou-Saleh

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Brain Imaging in Psychiatry

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M. T. ABOU-SALEH

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Contents

List of contributors 5

Editorial preface
M. T. ABOU-SALEH 7

Cranial computerised tomography in dementia of the Alzheimer type
A. BURNS 10

Computerised tomography in schizophrenia 15 years on
S. W. LEWIS 16

Colour plates

Magnetic resonance imaging and its applications in neuropsychiatry
J. A. O. BESSON 25

Psychiatry and the new magnetic resonance era
T. LOCK, M. T. ABOU-SALEH and R. H. T. EDWARDS 38

Magnetic resonance imaging and spectroscopy in schizophrenia
J. L. WADDINGTON, E. O'CALLAGHAN, C. LARKIN, O. REDMOND, J. STACK and J. T. ENNIS 56

The use and applications of single-photon emission computerised tomography in dementia
D. P. GEANEY and M. T. ABOU-SALEH 66

A study of depression in old age using single-photon emission computerised tomography
A. K. UPADHYAYA, M. T. ABOU-SALEH, K. WILSON, S. J. GRIME and M. CRITCHLEY 76

Positron emission tomography in the study of brain metabolism in psychiatric and neuropsychiatric disorders
C. J. BENCH, R. J. DOLAN, K. J. FRISTON and R. S. J. FRACKOWIAK 82

Cognitive brain potentials and their application
D. H. R. BLACKWOOD and W. J. MUIR 96

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Editorial Preface

M. T. ABOU-SALEH

The introduction of neuroimaging techniques for the study of brain structure and function has revolutionised the endeavour to elucidate the pathology of psychiatric disorder, the Holy Grail in psychiatry (Krishnan, 1990). Emil Kraepelin discovered the two major mental disorders, dementia praecox and manic–depression, and conceived their aetiology in brain pathology. It was Alois Alzheimer, however, his most successful student, who discovered the neuropathology of Alzheimer's disease. Sigmund Freud, who started his inquiries in brain science, lost faith and shifted to the study of the mind. Brain science and mind 'science' rapidly became odd bed fellows and parted company. The breakdown in communication fostered a mistrust in both parties, aborting endeavours of reconciliation. The evidence for the neuropathology of the 'functional' psychoses has, however, been inconclusive. It was the advent of brain-imaging techniques that rejuvenated brain sciences and modern neurosciences. The introduction of neuroimaging techniques, such as the electroencephalogram (EEG) in the 1920s and the whole-brain blood-flow techniques (Berger, 1929; Kety & Schmidt, 1948), antedated the discovery of psychotropic drugs. Pneumoencephalography was also applied to study brain structure in schizophrenia (Storey, 1966). The true methodological leap, however, was the introduction of computerised methods to construct three-dimensional images from two-dimensional data, enabling the development of computerised tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography (PET) and single-photon emission computerised tomography (SPECT).

The contents of this supplement are based on the proceedings of a symposium on this topic, complemented by reviews of other neuroimaging techniques to provide an up-to-date, state-of-the-art publication. Neuroimaging is a rapidly developing area in neurosciences, which we hope to have captured at a critical phase of development with an eye on the future.

Computerised tomography provided the means to visualise the live brain and to detect structural abnormalities; it has widespread applications in neurology, neurosurgery and psychiatry. In this supplement, Dr Burns reviews the CT technique in the differential diagnosis of dementia and examines the relationship between CT findings and the clinical picture of dementia of Alzheimer's type. He concludes that the main use of cranial CT techniques remains the exclusion of intracranial lesions, and while some CT findings correlate with the diagnosis of dementia, it is less useful in its differential diagnosis. Sophisticated techniques for scan analysis have shed light on the possible organic changes in depressive pseudodementia. Dr Burns concludes that the "CT scan is sleeping rather than dead".

The imaginative application of cranial CT to the study of schizophrenia (Johnstone *et al*, 1976) started a new era in the study of the biology of this disorder, resurrecting Kraepelin's concept of dementia praecox with the finding of CT brain abnormalities. Dr Lewis critically reviews the evidence 15 years on and examines the methodological problems in its application. Out of the 50 controlled studies in the world literature, he selects 21 studies that met stringent criteria for methodology for review. He concludes that there is relative enlargement of third and lateral ventricles and cortical sulci in some schizophrenic patients. These abnormalities appear to be long-standing, non-progressive and similar to the changes seen in neurodevelopmental disorders. He raises the important issue of the epidemiology of risk factors that determine these structural abnormalities as determined by the studies on control populations. As for the future, Dr Lewis suggests that although the baton has now passed to MRI, the CT technique will be used in conjunction with functional imaging techniques, such as PET and SPECT, "allowing us not just to see the machine, but its ghost as well".

Dr Besson, in a large review, provides a lucid exposition of the principles and the theory of MRI and its application in the study of neuropsychiatric disorders. This is illuminated by case studies in which the clinical characteristics are examined in relation to neuropathological, neurofunctional and therapeutic outcome in conditions such as Korsakoff's and Wilson's disease. He also introduces the concept of multimodality imaging of integrated anatomical–functional imaging with case studies of SPECT superimposed on MRI in Alzheimer's disease and superimposed PET on MRI in a case study of psychotic depression. The advantages of MRI over CT scan are exemplified in its ability to quantify images and identify regions of focal pathology through altered relaxation times. Finally, Dr Besson enriches his contribution by providing a multimodel approach to understand the MRI changes in the case of alcoholic brain disease.

The contribution by Dr Lock and colleagues follows, on psychiatry in the new magnetic resonance era, introducing the integrated magnetic resonance examination capable of acquiring anatomical, pathological and biochemical information in integrated clinical studies. Magnetic resonance spectroscopy (MRS) is depicted as the only technique in clinical medicine that provides non-invasive access to living chemistry. The advantages and disadvantages of this integrated examination are outlined, including the "human-machine" limitations and factors which affect the reproducibility of data. State-of-the-art clinical and animal studies are reviewed where developments relevant to psychiatry may be feasible and preliminary research findings are presented to illustrate relevant points. Dr Lock contends that this integrated MRI examination provides a non-invasive "biopsy", recognising the potential of this technique for "fishing in uncharted waters". The MRS technique, however, is compromised by its low sensitivity compared with other functional imaging techniques such as PET and SPECT.

Continuing with the MRI–MRS theme, Dr Waddington and colleagues provide a review and study of MRI–MRS in schizophrenia. The advantages of MRI over CT are highlighted: high resolution, good tissue contrast, multiplanar facility, and the lack of ionising and hazardous radiation. These advantages allow longitudinal prospective studies of first-episode patients, to examine the evolution of the disorder in relation to the structural and functional abnormalities. The precision of the technology has highlighted problems of methodology such as the subtle relationship between morphological changes and educational attainment and the extent of the normal range of these structural measures. The critical review of the quantitative and qualitative findings in schizophrenic populations is complemented by the results of MRI and MRS studies undertaken by Dr Waddington and colleagues: the MRI study showed a significant rate of morphological abnormalities in schizophrenic patients and phosphorus-31 MRS showed no spectral differences in the temporoparietal regions, except for evidence for increased intracellular pH, probably indicating localised tissue injury in this region.

The second section of this supplement is concerned with functional neuroimaging techniques. Dr Geaney and myself critically review the use and utility of SPECT in the diagnosis of dementia. SPECT, the most recently introduced neuroimaging technique, is a generally available and inexpensive method of measuring cerebral blood flow with evident usefulness in the management of dementia. The development of technitium-99m-labelled pharmaceuticals such as HMPAO to measure cerebral blood flow was a major advance in SPECT technology. SPECT studies using ^{99}Tc^{m}-HMPAO to investigate dementia are critically reviewed: the technique is a useful aid in the diagnosis of subtypes and the validity and significance of this requires full evaluation of outcome in follow-up studies to post-mortem of patients investigated by SPECT. Geaney *et al* (1990) have shown that patients with Alzheimer's disease had reduced rCBF in the posteroparietotemporal region compared with controls as determined by ^{99}Tc^{m}-HMPAO and SPECT. Central cholinergic stimulation with physostigmine produced a focal increase in regional cerebral blood flow in the posteroparietotemporal region in patients with Alzheimer's disease, but not in controls.

The study by Dr Upadhyaya and colleagues, however, casts doubt on the utility of SPECT in the management of dementia, with the finding that a discernible proportion of elderly patients with depressive illness show perfusion defects. These results may have important implications for the management and prognosis of depression in old age.

Positron-emission tomography (PET), the most powerful tool available for the measurement of brain function, is dealt with by Dr Bench and colleagues from the MRC Cyclotron Unit in Hammersmith Hospital in a large review describing its basic principles and application to the study of brain metabolism in neuropsychiatric disorders. A major focus of the review is on the development of resting-state metabolism studies by the application of specific activation paradigms and refined methods of data analysis. Studies have consistently shown regional abnormalities in the major psychoses as well as abnormalities specific to panic and obsessive–compulsive disorders traditionally thought to have a psychological aetiology. They conclude that future PET programmes will couple metabolic measures with activation paradigms of specific functional systems and studies using tracers for neuroreceptors will attempt to provide a parallel neurochemical basis for the metabolic profiles. These techniques will lead to major advances in elucidating the pathophysiology of psychiatric disorders as well as the delineation of clinical subgroups.

The application of cognitive brain potentials in psychiatry is reviewed by Drs Blackwood and Muir. The event-related potentials are selected from the on-going EEG activity by averaging epochs of EEG following repeated sensory or cognitive stimuli in their temporal relationship to the stimulus depicting sensory and cognitive components of perception. This technique furthers the understanding of the neuropsychology and the neurophysiology of psychiatric disorders and aids in their diagnosis. Studies of P300 responses suggest their utility in distinguishing subtypes of dementia, schizophrenia and depression.

The application of neuroimaging techniques in the study of psychiatric disorders has provided one of the most dramatic developments in biological psychiatry. There is little doubt that integrated, structural-functional techniques will lead to major advances in the understanding of the biology of psychiatric disorders, refining their classification and guiding management.

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Cranial Computerised Tomography in Dementia of the Alzheimer Type

ALISTAIR BURNS

The development of the non-invasive technique of computerised tomography (CT) in the mid-1970s revolutionised the clinician's ability to visualise brain structures *in vivo*. The main use of the CT scan was to exclude intracranial mass lesions such as cerebral tumours and haematomas. This remains its principal application in neurology and neurosurgery, but in psychiatry additional features such as cerebral infarctions, regional cerebral atrophy, ventricular enlargement and white-matter changes have provoked interest. This review outlines the technique of CT scanning, discusses its use in the differential diagnosis of dementia of the Alzheimer type (DAT), and comments on the relative contributions of cortical atrophy and ventricular enlargement to the clinical picture of DAT.

The technique

The CT scan apparatus consists of a radiation source emitting a tightly collimated beam which rotates in a gantry around the area of interest (in this case, the head). The head is placed between the X-ray source and a set of scintillation detectors. The amount of radiation registered by the detectors reflects the amount 'attenuated' by particular areas of the brain. Information obtained by the detectors is processed by a computer and results in a numerical output of numbers termed 'Hounsfield units'. Each scanned volume element (a voxel) is given an attenuation value depending on the degree of attenuation in each structure within the voxel. The numerical output is transferred to a 'grey scale' and each voxel is represented by a two-dimensional pixel (picture element cell) on a plain X-ray film. On the grey scale, black represents areas where very little attenuation of the X-ray beam has taken place (low-density structures such as cerebrospinal fluid (CSF)) and white represents regions where attenuation is high (high-density structures such as bone). Between these two extremes, areas of medium density such as brain tissue appear grey.

A major technical drawback of the CT scan is 'partial-volume' artefact. It is not easy to appreciate, but a brain slice visualised in a two-dimensional CT image represents a three-dimensional structure. Each slice is up to 10 mm thick, and so in areas at the interface between CSF and brain, the pixel represents the average attenuation number of both brain and CSF. Therefore the walls of the lateral ventricles cannot be absolutely defined and depend, to a certain extent, on the slice thickness and resolution of the scanner. Computer algorithms which assess ventricular size direct from the numerical output of the scanner, independent of conversion to the grey scale, circumvent this problem.

The amount of radioactivity involved in the standard cranial CT scan is moderate and the gonadal radiation dose has been calculated to be about two-thirds that of a full set of skull X-rays (Gyldensted, 1977).

Differential diagnosis

As stated, the main use of CT is in the detection of intracranial mass lesions. It is of particular importance therefore in the investigation of subjects presenting with cerebral organic disease such as dementia. Studies of the frequency with which potentially treatable causes for a dementia syndrome are discovered in the course of its investigation have been reviewed (Byrne, 1987; Philpot & Burns, 1989). CT scanning tends to be reserved for cases in which there is a high index of suspicion, but as scanners become more commonplace and the CT scan becomes more widely used, a more representative picture of the prevalence of potentially treatable causes of dementia becomes available. For example, Jacoby & Levy (1980) scanned 40 demented patients on the basis of a "reasonable clinical probability" that they suffered from senile dementia of the Alzheimer type (SDAT) and found one to have a corpus callosum glioma and another a subdural haematoma. The available evidence suggests that 5–10% of demented patients will have mass lesions – the yield in younger patients scanned because of a particular suspicion of intracranial pathology will obviously be higher than an older group scanned 'routinely'.

The other main use of the scan is to detect focal lesions suggestive of cerebral infarction, and the ability of the scan to differentiate vascular from degenerative dementia has been examined. Loeb &

Gandolfo (1983) evaluated the ability of the Hachinski score (Hachinski *et al*, 1975) to separate vascular and degenerative dementia as seen on CT. The Hachinski score, although originally validated using blood-flow techniques, has been validated neuropathologically (Rosen *et al*, 1980; Wade *et al*, 1987) and so its use to differentiate the two types of dementia seems justified. Loeb & Gandolfo (1983) found that the Hachinski score agreed with the CT findings of DAT (ventricular enlargement and cortical atrophy) in 69% of cases and with the CT findings of vascular dementia (multiple low-density areas) in 95%. Cummings *et al* (1987) found focal lesions in 14 out of 15 cases of vascular dementia while none of 30 DAT subjects had such lesions. Erkinjuntti *et al* (1987) found one or more cerebral infarcts in 70 of 79 subjects with vascular dementia and only one out of 65 with DAT.

However, care must be taken in assessing the differentiating ability of CT, as many diagnostic schemes (e.g. DSM-III-R) now include the results of CT scans in their diagnostic criteria. It is therefore a circular argument to define DAT or multi-infarct dementia (MID) using such a scheme and then to report the proportion in each diagnostic group with vascular lesions on CT.

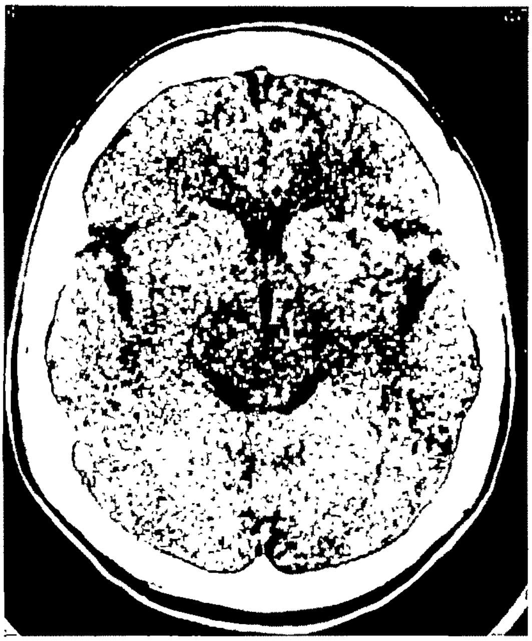

FIG. 1 Normal CT scan showing anterior horns of lateral ventricles, third ventricle and Sylvian fissures.

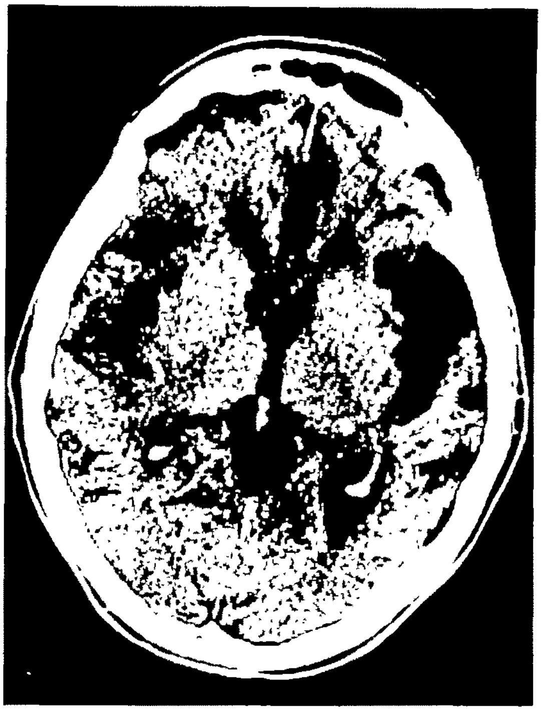

FIG. 2 CT scan of a subject with dementia, showing enlargement of the interhemispheric fissure, third ventricle and massive enlargement of the Sylvian fissures.

White-matter changes (periventricular lucency) have been described in the CT scans of demented patients and normal elderly subjects. It seems to be related to cognitive decline and motor abnormalities and may reflect underlying amyloid angiopathy (Joyce & Lishman, 1988).

Non-specific changes on CT scans may be seen in other conditions that give rise to a dementia syndrome. Chronic alcoholics show evidence of cortical atrophy in ventricular enlargement before cognitive impairment is clinically apparent (Lishman, 1987). In Huntington's disease, atrophy of the frontal regions occurs (frontotemporal atrophy, enlargement of the third ventricle or anterior horn) along with caudate atrophy (Sachs *et al*, 1983). Parkinson's disease is associated with both cortical and subcortical atrophy, the latter being particularly associated with cognitive deficits (Sroka *et al*, 1981). Changes on CT scans may also be seen in subjects with so-called depressive pseudodementia – ventricular brain ratio (VBR) is increased and tissue density decreased (Pearlson *et al*, 1989) and a test of motor speed, which does not improve after treatment for depression, has been shown to be associated with VBR (Abas *et al*, 1990).

The results of investigations involving CT scanning in DAT can be divided into three broad categories – assessment of cerebral surface atrophy (cortical or sulcal atrophy), assessment of ventricular size (subcortical or central atrophy) and CT studies involving the measurement of brain density. Figs 1 and 2 exemplify the differences found between demented and healthy subjects on CT.

Cortical atrophy in DAT

There is progressive cortical atrophy with increasing age (Jacoby *et al*, 1980) which appears to accelerate after the age of 60 (Zatz *et al*, 1982*a*,*b*). There is overwhelming evidence that cortical atrophy in DAT is greater than in normal ageing (Huckman *et al*, 1975; Jacoby & Levy, 1980; Soininen *et al*, 1982). Jacoby & Levy (1980) studied 40 SDAT patients and compared them with 50 age-matched healthy volunteers. The patients had higher atrophy ratings than the controls, and while there was a positive correlation between age and atrophy in the normal population, none existed in the demented group. The lack of an association between age and atrophy in dementia was replicated by Soininen *et al* (1982) in 57 subjects and by Leys *et al* (1989) in 30 patients.

Correlations between cerebral atrophy and cognitive impairment have also been found – De Leon *et al* (1980) found an association between a number of psychological tests and a visual four-point rating of cortical sulci. Ernest *et al* (1979) found similar significant correlations but the population under study was not well characterised and consisted of elderly people living independently, some of whom had cognitive impairment. Merskey *et al* (1980) found a significant negative association between cognitive score and atrophy of the Sylvian fissures but not atrophy on the cuts of the scan above the lateral ventricles. Claviera *et al* (1977) rated cortical atrophy and made a global psychometric assessment, finding a non-statistically significant association between the two. They described one of the fundamental findings in CT scanning concerning demented patients and normal controls, the 'bipartite enigma' – namely that some demented patients had normal CT scans and some normal controls had CT scan indices well into the range associated with dementia.

Some studies have looked for, but not found, a correlation between sulcal size and cognitive dysfunction (Roberts & Caird, 1976; De Leon *et al*, 1979; Drayer *et al*, 1985). Kido *et al* (1989) assessed the temporal horn and Sylvian fissures in 39 DAT patients and 29 controls. They found dilatation of the former to be a specific indicator of DAT but lacking in sensitivity, while the latter was a sensitive indicator of dementia but was not specific.

Ventricular enlargement in DAT

Ventricular size can be measured more accurately than sulcal widening by means of mechanical planimetry and computer programs have been developed to assess ventricular volume (Jernigan *et al*, 1979; Zatz *et al*, 1982*a*,*b*). As with cortical atrophy, ventricular size increases with age, accelerating in the over-60s (Takeda & Matsuzawa, 1984). DAT patients have significantly larger ventricles than age-matched controls (Jacoby & Levy, 1980; Soininen *et al*, 1982; Drayer *et al*, 1985). Generally speaking, correlations between ventricular enlargement and cognitive function are stronger than between cortical atrophy and cognition (e.g. Eslinger, 1984).

Drayer *et al* (1985) studied 60 early-onset DAT cases (mean age 61 years) and found statistically significant associations between linear measures (but not visual assessments) of ventricular size and scores on the Mini Mental State Examination (MMSE), score on the Wechsler Adult Intelligence Scale (WAIS) and an aphasia score. Leys *et al* (1989) also studied 30 cases of early-onset DAT (mean age 63 years) but found no association between lateral ventricular enlargement and MMSE scores. However, a highly significant association occurred between the third-ventricular size and anterior-horn enlargement and both the MMSE and a global deterioration scale (Reisberg *et al*, 1982).

The majority of other studies have examined elderly subjects. Roberts & Caird (1976) scanned 66 patients with a mean age of 77 years and found associations between ventricular size and both a cognitive and behavioural rating. The inclusion of subjects with normal cognitive function and the lack of criteria given for inclusion in the study make the findings difficult to compare with those of other studies. Jacoby & Levy (1980) found a weak negative correlation between planimetric measures of ventricular size and the digit–symbol substitution test, but no association with memory, disorientation or apraxia. De Leon *et al* (1980) studied 43 patients (mean age 70 years) with SDAT using 37 different tests of cognition. They arranged the scans in order of the severity of ventricular enlargement and found, using this procedure, that ventricular size had a strong negative correlation with cognitive impairment. A correlation between VBR and cerebrospinal fluid acetylcholinesterase activity has also been found (Pearlson & Tune, 1986).

Studies have shown that serial CT scans on the same patient may improve diagnostic certainty, as ventricular size increases significantly over time in DAT subjects but not in normal controls (Luxenberg *et al*, 1987; De Leon *et al*, 1989).

The third ventricle has been examined separately in a number of studies. Creasey *et al* (1986) found it to be larger in male DAT subjects compared with females and there is general agreement that it is increased in demented patients compared with normal controls (Soininen *et al*, 1982; Creasey *et al*, 1986; Leys *et al*, 1989). The size of the third ventricle has been shown to correlate with age, age of onset of dementia and cognitive impairment in early-onset DAT.

Results with computerised methods of analysis

More recently, computerised methods have been developed which estimate ventricular size (Baldy *et al*, 1986). Many of these assess CSF volume in the brain, comprising both ventricular size and cortical atrophy. As the former contributes most to total intracranial CSF, these studies are considered here. Zatz *et al* (1982*a*,*b*) and Jernigan *et al* (1979) reported a method in which a mathematical algorithm was used, based on the proportion of CSF and brain and their respective densities, to estimate volume of intracranial fluid. The model accounted for the partial-volume artefact by assigning each four-pixel area to either brain or CSF depending on its mean value. Zatz *et al* (1982*a*,*b*) studied 123 normal subjects (aged 23 to 88) and found that measures were roughly constant till age 60 and then increased markedly thereafter.

Albert *et al* (1984*a*) used computer programs to assess CT scans – one assessed brain density in the whole slice while the other assessed fluid volume. Basically, these compared a 169-pixel area of standard brain tissue to areas of four pixels throughout the brain slice, assigning each to either CSF or brain. In eight patients with pre-senile dementia and ten healthy controls, CSF volume successfully predicted group membership in 89% of cases – linear CT measurements predicted membership in 79%. In an accompanying paper, the same group (Albert *et al*, 1984*b*) looked at the same CT measures in 13 elderly patients with DAT and 18 age-matched controls. The linear measures predicted group membership (patient or control) in only 67% of cases. The computerised measures were able to predict group membership with more success (77%) using the mean density numbers on the slice where the maximum width of the lateral ventricles was seen. If the results of analysis of a second slice (fluid volume on the slice of the maximum width of the third ventricle) were added, group membership was predicted in 94%.

Creasey *et al* (1986) reported 34 different CT measures, including ventricular areas, total CSF space, white and grey matter, in 75 subjects. Men and women were analysed separately as initial analyses showed that the former had significantly bigger heads and higher CSF and brain volume. A number of differences were found in the CT measures between the demented and control groups. Volume of the third ventricle was negatively correlated with the Mattis dementia score (Coblentz *et al*, 1973) and WAIS in the males. Possible sources of error in this study included the limitation of the analysis to a 50 mm horizontal segment (to avoid 'beam-hardening', but also possibly underestimating cortical atrophy) and the inclusion of areas of partial volume being wrongly categorised as white matter.

These studies, taken together, suggested that computerised CT assessments are helpful in the differentiation of patients with DAT (both young and old) from age-matched controls. However, the numbers of patients involved are small, and the computer programs complicated and therefore possibly not routinely clinically helpful. The successful prediction of group membership is only slightly better than that found using planimetric measures (Jacoby & Levy, 1980; Damasio *et al*, 1983). All the various computerised assessments have been shown to be highly correlated with more traditional linear and visual ratings of CT scans. A further drawback of the method is that the CT analyses described are complex and have not necessarily been anatomically validated – it seems premature therefore to draw definitive conclusions when interpreting these results.

Measurements of brain density

Conversion of the raw numerical data of the CT scan to a grey scale involves loss of information. A computerised program that measures CSF volume includes a maximum amount of information by measuring attenuation numbers (in Hounsfield units). Another method which utilises these data is to measure density numbers in brain parenchyma.

Naeser *et al* (1980) were among the first to employ such a system. They examined patients with both presenile and senile dementia, comparing them with age-matched controls. They found that the density numbers in the centrum semiovale slice were lower in the demented group. This effect was independent of the presence of cortical sulcal enlargement on the same slice, but the effect of ventricular size was not considered. Zatz *et al* (1982*a*,*b*) found that attenuation numbers correlated with age and were independent of atrophy, while Schwartz *et al* (1985) found no association between age and attenuation values. Differences in methods, including failure to correct for head and slice size, probably explain this.

Bondareff *et al* (1981) studied regional density in 15 brain regions by comparing 25 patients with SDAT and 29 normal volunteers. The rationale behind regional measurements was to examine whether they would confirm those found histopathologically. The sample was the same as that of Jacoby & Levy (1980). Fifteen brain regions were studied and mean density numbers were found to be significantly lower in the patient group in the medial temporal lobe, anterior frontal lobe, and caudate nucleus. This was independent of ventricular size. The authors argued that, with the exception of the caudate nucleus, these corresponded to the areas affected preferentially in DAT, as proven in neuropathological studies.

Naguib & Levy (1982) reported a follow-up of 40 SDAT patients for a mean of 29 months. During that period, 27 had died. Those who had died had significantly lower attenuation numbers in the right parietal region, confirming that parietal-lobe involvement was a poor prognostic sign in DAT (McDonald, 1969). Colgan (1985) followed 40 patients with SDAT (mean age 78 years) for six months during which time 10 died. Decreased attenuation numbers were found bilaterally in the parietal and occipital lobes and in the left thalamic region of the non-survivors. Both these studies suggested that mortality in SDAT was associated with decreased tissue density in posterior brain regions – parietal and occipital lobes. One difficulty in interpreting results from such CT studies is the lack of precise anatomical definition of CT brain regions. Thus, it is possible that the occipital lobe in one study was very similar to the posterior parietal lobe in another study. Also, head size was not taken into account and this has been shown to affect attenuation numbers (Pearlson *et al*, 1989).

Conclusions and future prospects

Computerised tomography has been available for about 15 years, and during that time more technologically advanced CT scanners and improved methods of scan analysis have been developed. However, the main use of cranial CT remains the exclusion of intracranial mass lesions by non-invasive means (or relatively non-invasive if contrast enhancement is employed). The technology has allowed for the evaluation of the brain in normal ageing, which, hitherto, had only been possible at autopsy. However, the changes of cerebral atrophy (both cortical and subcortical) seen in DAT have been shown not to be diagnostic and as such the technique may have been seen by many to be disappointing. Initial optimism concerning the CT scan and its contribution to the diagnosis of depression and dementia must now be tempered (Jacoby, 1981). Findings on CT correlate well with diagnosis but less well within diagnosis. Significant overlap occurs in scan appearances between normal and demented elderly subjects. The detection of regional atrophic changes, clinically silent cerebral infarctions and white-matter changes are all helpful in the differential diagnosis of a dementia syndrome. More sophisticated techniques for scan analysis have shed light on possible organic changes in depressive pseudodementia (Pearson *et al*, 1989) and the use of serial CT scans in individual patients may improve diagnostic accuracy and shed light on the progress of DAT. One might be forgiven for saying that currently the CT scan is sleeping rather than dead.

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Computerised Tomography in Schizophrenia 15 Years On

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X-ray computerised tomography (CT) has revolutionised diagnostic radiology, particularly neuroradiology, since its inception (Houndsfield, 1973). It has been used widely in the systematic examination of brain structure in schizophrenia since the first study, 15 years ago, by Johnstone *et al* (1976). Several good reviews of the findings appeared in the mid-1980s (e.g. Reveley, 1985*a*; Shelton & Weinberger, 1986). Since then, although the spate of published studies has slowed, the quality of more recent published studies has in general been higher than the earlier ones, and it is time to look at the field again. This review examines the methodological pitfalls in CT research in schizophrenia and then attempts to draw some conclusions in the light of these.

Questions of methodology

At its simplest level, the usual CT study of schizophrenia involves scanning a sample of schizophrenic patients, scanning a sample of non-schizophrenic controls, and measuring various parameters of the images obtained. However, early on it became clear that any differences seen between patient and control groups were in the main quantitative rather than qualitative. Moreover, these changes were usually minor in degree, with considerable overlap between groups. Studies were soon seen to vary widely in the reported prevalence of abnormal findings and the most reasonable explanation of this lay in variation in the selection of patients, the choice of controls, and the methods of measurement.

Most studies have used operational diagnostic criteria to define the patient group, but have still differed widely in patients' demographic and treatment characteristics. There is now much evidence that these factors do influence the prevalence of abnormalities found (Luchins, 1982; Luchins & Meltzer, 1986; Owen & Lewis, 1986) and epidemiological samples such as first-episode patients (Turner *et al*, 1986) or consecutive admissions from a defined catchment area (Iacono *et al*, 1988) are to be preferred.

The use of exclusion criteria also vary. Those more commonly applied are histories of neurological disease, mental retardation, an upper age limit, and concurrent physical illness. Evidence of heavy alcohol consumption is also a common exclusion criterion, although definitions vary from 'abuse' (Largen *et al*, 1984) to 'alcoholism' (Bishop *et al*, 1983); some studies only exclude alcohol abuse if of "aetiological significance to the psychiatric disorder" (Williams *et al*, 1985) despite evidence that it is a potent confounding variable however defined (Ron, 1983). Elsewhere, exclusion criteria have comprised female gender, abnormal findings on electroencephalography (EEG), left-handedness and others whose theoretical justification is often unclear.

The rigorous selection of controls is at least as important. The ideal control group would seem to be healthy volunteers matched at least for age and sex, prospectively scanned on the same machine during the same period. Psychiatric screening and determination of alcohol consumption is needed. Any exclusion criteria used in the patient group should also be used in the controls. To date, most studies have not used healthy volunteer controls. Usually, other non-schizophrenic patient groups are used: typically neurological patients with histories of minor head injury or headache. Often this practice is further confounded by including in the control group only those subjects whose scan has first been passed as 'normal' by a radiologist.

Although the use of normalised neurological controls has been defended (Raz *et al*, 1988), Smith & Iacono (1986) reviewed the literature and showed that reported ventricular size was significantly smaller in neurological control groups than in healthy volunteer control groups. The use of neurological controls might thus be a major source of type 1 error. This view was supported by these authors' own prospective study. This used both types of controls and showed that comparisons with the neurological control group led to an overestimate of the prevalence of abnormalities in the schizophrenic patients (Smith *et al*, 1988).

The third source of variation between studies is in the techniques of measurement used. The structures most commonly measured are the lateral cerebral ventricles. The most popular index of lateral ventricular size has been the ventricle:brain ratio

(VBR), first proposed by Synek & Reuben (1976). The VBR expresses the area of the lateral ventricles, as measured on the transverse CT slice which best shows them, as a ratio of the whole brain area measured on the same slice. Its rationale is that, since people with large heads will normally have large ventricles, this ratio will control for differences in head size. It assumes firstly that there is a linear relationship between ventricle size and head size in the general population, and secondly that head size in schizophrenic patients is no different from that in controls. In fact, neither assumption is watertight (Zatz & Jernigan, 1983; Harvey *et al*, 1990) although VBR does seem to be a valid indicator of the total volume of the lateral ventricles (Reveley, 1985*b*).

Actual measurement of areas has been performed in two ways. Mechanical planimetry uses an articulated device to trace manually around the edge of the structure on the photographic film. However, this relies on visual inspection and, particularly where ventricles are small, the grey areas at the interface between fluid and brain can give rise to real problems in deciding where the edges of the ventricle actually lie: the so-called partial-volume effect. This method has been largely superseded by various automated or semi-automated techniques. These have theoretical and practical advantages in that they use the original digital CT data and, although the partial-volume problem is not wholly overcome, have very high inter-rater reliability (Reveley, 1985*b*).

An additional confounding factor is the question of instability of measurements over time on the same scanner, so-called 'scanner drift'. This was a major problem with many early systems, although experimental and control scans should still be made concurrently to ensure against change in density measures over time.

Are there really CT changes in schizophrenia?

There are now over 50 controlled studies in the world literature which have examined some aspect of brain structure in schizophrenic patients using CT. The results are widely divergent, as was already apparent after the first few studies (Luchins, 1982). The use of stringent methodology to exclude possible artefact is important in reaching a useful conclusion. Therefore, this review considers only those studies in which controls were prospectively ascertained healthy volunteers, scanned concurrently with the patient group.

The 21 studies meeting these criteria are listed in Table I. Most of these studies have been published in the last five years. In comparison with less well controlled studies, a relatively high proportion of these studies failed to show significant CT abnormalities in schizophrenic patients. Of the 21 studies listed in Table I, nine could not demonstrate lateral ventricular enlargement in the patient group and a further three showed this at only marginal degrees of statistical significance. It should be noted that the statistical power of the individual study is not a good predictor of the likelihood of finding an effect: five of the 12 studies with more than 50 subjects in total could not demonstrate an effect, compared with four of the nine smaller studies.

Besides lateral ventricular size, studies have increasingly looked for differences in other cerebral fluid spaces, in particular enlargement of the third ventricle and cerebral cortical sulci. As can be seen from Table I, several studies have now reported an enlarged third ventricle or enlarged cortical sulci in the absence of significant lateral ventricular changes. Other claims, such as enlarged cerebellar sulci, widened Sylvian and interhemispheric fissures, and asymmetry of occipital pole size, have not been well replicated.

A few studies have attempted to compare radiodensity measures between patients and controls. This is an area fraught with methodological difficulties (Jacobson *et al*, 1985) and, although one carefully executed study found reduced left-hemisphere density in schizophrenic twins compared with their non-schizophrenic identical cotwins (Reveley *et al*, 1987), Pearlson *et al* (1989) found no differences. The continuing disparity between studies again points to the likelihood of methodological confounding factors.

Although the studies reviewed had as their minimum requirement a control group of prospectively scanned healthy volunteers, the decision about which variables should be matched between patients and controls is still at issue. Certainly, age and sex should be matched. In addition, evidence is accruing that other demographic factors can influence measures of brain structure: social class (Pearlson *et al*, 1989), height, ethnicity (Nimgaonkar *et al*, 1988) and educational level (DeMyer *et al*, 1988), for example. The effect of such variables has been highlighted by the controversial claims of reduced head size in schizophrenic patients. The initial report of this proved to be explainable on the basis of differences in height (Andreasen *et al*, 1986). Although a subsequent study which controlled for height still found smaller head size, significant social-class effects were present (Pearlson *et al*, 1989).

Another issue in need of further clarification is the specificity of reported abnormalities to schizophrenia. Most of the changes in schizophrenia have also been reported in other severe 'functional' psychiatric

TABLE I

Twenty-one CT studies comparing schizophrenic patients with prospectively ascertained healthy volunteers

	No. of schizophrenic patients	*No. of healthy controls*	*Enlargement of*			*Comments*
			lateral ventricles	*third ventricles*	*cortical sulci*	
Johnstone *et al* (1976)	13	8	+			Long-stay patients
Jernigan *et al* (1982)	29	33	–			
Nyback *et al* (1982)	23	48	+	(+)		Linear measures used
Reveley *et al* (1984)	21	18	–			Schizophrenic versus healthy monozygotic twins: earlier study showed larger ventricles in subsample
Schulsinger *et al* (1984)	7	13	+			All subjects had schizophrenic mothers
Pearlson *et al* (1985)	19	19	(+)			
DeLisi *et al* (1986)	25	20	(+)		–	
Turner *et al* (1986)	30	26	+			First-episode patients
Losonczy *et al* (1986)	28	21	+			All subjects male
Shima *et al* (1985) Kanba *et al* (1987)	37	37	–	+		
Kemali *et al* (1987)	50	25	+			
Smith *et al* (1988)	30	30	–	+	+	
Iacono *et al* (1988)	31	44	–	(+)	–	First-episode, community-based samples
Stahl *et al* (1988)	8	8	–	+	(+)	Severely ill patients: no quantitative measures
Pfefferbaum *et al* (1988)	45	57	(+)	+	+	Patients all male; controls of both sexes
Pearlson *et al* (1989)	50	87	+			Patients selected for chronic unemployment. No brain-density differences found
McCarley *et al* (1989)	9	9	–	+	+	
McCreadie *et al* (1989)	27	27	–	–	+	First-episode patients; two scanners used
Andreasen *et al* (1989)	110	75	+	–	–	Ventricular enlargement confined to males
Williamson *et al* (1989)	15	18	–			
Harvey *et al* (1990)	37	50	+			

+ Statistically significant enlargement found in patients compared with controls.
(+) Marginal statistical significance: usually only on one-tailed test.
– Variable examined, but no enlargement found in patients.

disorders, including affective disorders, obsessive–compulsive disorder and anorexia nervosa.

Focal lesions

The minor degrees of enlargement of ventricles and sulci found in the majority of studies would not usually be reported as abnormal by most clinical radiologists. However, there are a handful of reports in the literature of gross focal brain lesions in schizophrenia, as demonstrated by CT: aqueduct stenosis (Reveley & Reveley, 1983), arachnoid and septal cysts (Kuhnley *et al*, 1981; Lewis & Mezey, 1985), and agenesis of the corpus callosum (Lewis *et al*, 1988).

Three larger studies enable an estimate to be made of the prevalence of such focal lesions on CT in schizophrenia. Owens *et al* (1980), in their series of 136 schizophrenic patients, found "unsuspected intracranial pathology" as a focal finding on CT in 12 cases (9%), excluding lesions due to leucotomy. Five of these 12 were aged over 65. Lewis (1987) examined a series of 228 Maudsley Hospital patients who met Research Diagnostic Criteria (RDC) for schizophrenia and who had been consecutively scanned for clinical reasons. Patients with a history of epilepsy or intracranial surgery, or who were aged over 65 at the time of scan, were excluded. The original scan reports were examined and the films of those not unequivocally normal were reappraised by

TABLE II
Laterality, locus and nature of focal lesions found on CT in 13 of 228 schizophrenic patients

Site	*Number*	*Nature of lesion*
Right-sided		
frontal	1	Low-attenuation
parietal	3	Calcified mass (1), porencephalic cyst (1), low attenuation (1)
temporal	1	Old abscess cavity
Left-sided		
frontoparietal	1	Low attenuation
temporal	3	Arachnoid cyst (2), calcification (1)
occipitotemporal	1	Arachnoid cyst
Midline	1	Septal cyst
Bilateral	2	Occipital low attenuation (1), parasagittal calcification (1)

a neuroradiologist blind to the original report. In 41 patients the scan showed a definite intracranial abnormality. This was in the nature of enlarged fluid spaces in 28 cases, but in 13 patients (6%) there was a discrete focal lesion. These 13 lesions varied widely in location and probable pathology (Table II), although left temporal and right parietal regions were most commonly implicated. The third study (Lewis & Reveley, in preparation) was an attempt to examine a geographically defined sample of schizophrenic patients, ascertained as part of a large, multidisciplinary survey (Brugha *et al*, 1988). All Camberwell residents who, on a particular census day, were aged 18-65 and were in regular contact with any psychiatric day service were approached. Of 120 eligible people, 83 consented to CT and psychiatric interview. Fifty of these met RDC for schizophrenia or schizoaffective disorder. In four of these 50 patients (8%) were found clinically unsuspected focal lesions: low density in the right caudate head; a left occipitotemporal porencephalic cyst; low-density regions in the right parietal lobe; agenesis of the corpus callosum (described further by Lewis *et al* (1988)). None of 50 matched healthy volunteers showed focal pathology on CT.

Given the differences in the nature of the patient samples, these three studies are in rough agreement about the prevalence of unexpected focal abnormalities on CT: between 6% and 9%. From the practical viewpoint of the referring clinician, it should be noted that the discovery of these abnormalities led to no change in the management of the patient in the great majority of cases. This was because most of the lesions appeared to be non-progressive and in the nature of developmental anomalies. From the locationist perspective, the contents of Table II will be disappointing: the brain regions involved varied widely.

Despite intriguing case reports of familial association (Francis, 1979), the prevalence of basal ganglia calcification on CT was not found to be raised in schizophrenia in two recent large studies (Casanova *et al*, 1990; Philpot & Lewis, 1990).

Clinical correlates of CT abnormalities

Given that a minority of schizophrenic patients probably do have modest enlargement of lateral and third ventricles, and cortical sulci, on CT, can this subgroup be identified in terms of a particular clinical picture? Table III attempts to summarise studies that have compared patients with abnormal versus normal CT, in terms of lateral ventricular size, on a range of clinical variables. Such studies use a strategy which does not strictly require a normal control group, although the dividing line between normal and abnormal ventricular size is necessarily arbitrary, often being expressed in terms of greater than one or two standard deviations of a patient or control group mean. The distribution of VBR in most patient groups is positively skewed, although there is little evidence to suggest this is in reality a bimodal distribution.

For most clinical variables mooted at one time or another to be related to ventricular enlargement, there is little in the way of convincing replication. The appealing notion that negative symptoms and poor treatment response are characteristics of schizophrenia with ventricular enlargement does not have much objective support. The only associations that have more positive than negative replications are those of tardive dyskinesia and, most particularly, impaired performance on neuropsychological tests, although the specific areas of cognitive impairment tend to vary from study to study.

There is some evidence that abnormalities on CT scans are actually predicted by an atypical clinical picture. Harvey *et al* (1990) found that their subgroup of unspecified functional psychoses had particularly enlarged ventricles, and unusual symptoms such as delusional misidentification are commonly associated with CT abnormalities: 21 of the 23 cases of Capgras syndrome reported with neuroimaging data have shown abnormalities (references available from author) (Lewis, 1989*a*). In the CT study of 228 schizophrenic patients referred to earlier (Lewis, 1987), the subgroup with unequivocally abnormal scans had a significantly greater frequency of changing clinical diagnosis, suggesting an atypical presentation.

TABLE III
Clinical correlates claimed for ventricular enlargement in schizophrenia: 41 studies

Clinical feature	*Significant correlation found*	*No significant correlation found*
Poor pre-morbid adjustment	3, 17, 19, 39	7, 10, 22, 23, 27
Older age at onset	7	10, 17, 18, 19, 22, 26, 27, 31, 35
Duration of illness before scan	22	2, 7, 10, 11, 16, 17, 18, 21, 23, 25, 26, 27, 29, 31, 37*, 38, 41
Fewer positive symptoms	7, 13, 35	8, 10, 17, 18, 20, 23, 25*, 27, 31, 32, 34, 37, 38, 40
More negative symptoms	17, 19, 22, 34, 39	7, 10, 13, 18, 20, 23, 27, 31, 35, 36, 37, 38, 40
Poor treatment response	4, 12, 13, 26, 33	10, 15*, 32, 36
More tardive dyskinesia	9, 18, 30, 38	17, 27
Impaired neuro-psychological test performance	1, 5, 6, 7, 14, 18, 22, 28, 38, 40, 41	17, 24, 31

*Study showed significant effect in *opposite* direction.
1. Johnstone *et al* (1976)
2. Weinberger *et al* (1979)
3. Weinberger *et al* (1980*a*)
4. Weinberger *et al* (1980*b*)
5. Donnelly *et al* (1980)
6. Golden *et al* (1980)
7. Andreasen *et al* (1982)
8. Bishop *et al* (1983)
9. Luchins *et al* (1983)
10. Nasrallah *et al* (1983)
11. Kling *et al* (1983)
12. Schulz *et al* (1983)
13. Luchins *et al* (1984)
14. Adams *et al* (1984)
15. Smith *et al* (1984)
16. Oxenstierna *et al* (1984)
17. Williams *et al* (1985)
18. Owens *et al* (1985)
19. Pearlson *et al* (1985)
20. DeLisi *et al* (1986)
21. Obiols Landrich *et al* (1986)
22. Kemali *et al* (1986)
23. Pandurangi *et al* (1988)
24. Romani *et al* (1987)
25. Farmer *et al* (1987)
26. Gattaz *et al* (1988)
27. Swayze *et al* (1988)
28. Lawson *et al* (1988)
29. Rossi *et al* (1989)
30. Kaufmann *et al* (1986)
31. Pfefferbaum *et al* (1988)
32. Losonczky *et al* (1986*a*,*b*)
33. Pandurangi *et al* (1989)
34. Moscarelli *et al* (1989)
35. Pearlson *et al* (1989)
36. McCreadie *et al* (1989)
37. Kaiya *et al* (1989)
38. Johnstone *et al* (1989)
39. Van Kammen *et al* (1988)
40. Keilp *et al* (1988)
41. Williamson *et al* (1989)

One determinedly negative association worth noting is that of duration of illness. The degree of ventricular enlargement is convincingly not a function of how long the patient has been ill, nor of how long he has been treated.

The natural history and aetiology of CT abnormalities

The lack of an association between length of illness and degree of lateral ventricular enlargement suggests that this enlargement is not progressive, neither in the sense of reflecting a neurodegenerative disorder, nor as being an artefact of continuing treatment or institutional care. This view receives support from the demonstration of significant ventricular enlargement in young, first-episode patients (Turner *et al*, 1986). Direct evidence for the non-progressive nature of ventricular enlargement is now available from several follow-up studies which have rescanned patients after periods of up to seven years. Three such studies have reported no change in ventricular size (Nasrallah *et al*, 1986; Illowsky *et al*, 1988; Reveley *et al*, 1988), although a fourth did find a significant enlargement from baseline VBR in rescanned schizophrenic patients versus healthy controls (Kemali *et al*, 1989). Obviously, it is important in such studies to control rigorously for known confounding variables, such as heavy drinking.

The implication from the apparently non-progressive nature of the CT scan changes, which is reinforced by the increasing number of reports of congenital focal lesions as noted above, is that they represent early neurodevelopmental abnormalities. These could result from the action of inherited factors, or from environmental insults, or a combination of the two. Clues about this have been sought by trying to show an association between CT abnormalities and indicators either of a genetic diathesis or of early neurodevelopmental damage: specifically, manifest family history of psychiatric disorder, or history of pregnancy and birth complications.

With regard to genetic factors, the original hypothesis, that ventricular enlargement was largely confined to those patients with no evident family history (Reveley *et al*, 1984; Murray *et al*, 1985; Lewis *et al*, 1987), is now looking outdated. Of 13 studies looking for this association, four have reported a significant inverse correlation between ventricular size and positive family history (Reveley *et al*, 1984; Cazullo *et al*, 1985; Turner *et al*, 1986; Romani *et al*, 1987). One study found a positive correlation (Nasrallah *et al*, 1983) and one a significant curvilinear correlation (Owens *et al*, 1985). Most reports have found no relationship (Pearlson *et al*, 1985; Farmer *et al*, 1987; Kemali *et al*, 1986; Nimgaonkar *et al*, 1988; Johnstone *et al*, 1989; Pearlson *et al*, 1989; Kaiya *et al*, 1989). However, many of these studies lack adequate statistical power, and all are open to the problems of the family history method, with varying definitions, uncertain reliability, and variable family sizes. In a study designed to overcome the problem of limited power, Owen *et al* (1989) compared ventricular size in 48 schizophrenic patients with a history of treated major psychiatric disorder in a first-degree relative, 48 schizophrenic patients with no such history in first- or second-degree relatives, and the same number of healthy controls. The three groups were matched for age and sex. Significant ventricular enlargement was found in those without a family history, as predicted. However, those patients with a family history positive for schizophrenia also showed significant enlargement, against expectations, whereas a family history of affective disorder was associated with normal ventricular size.

Several studies have demonstrated a raised rate of obstetric complications in the histories of schizophrenic patients compared with other psychiatric patients, well siblings, or unrelated controls (Lewis, 1989*b*; Eagles *et al*, 1990). This has led to the hypothesis that obstetric complications could be a risk factor for schizophrenia with abnormal CT findings.

Like the assessment of family history, the assessment of past obstetric complications is dogged by problems of definition and, in most cases, relies on the memory of an informant, although a recent validation study has shown that such data can be reliable (O'Callaghan *et al*, 1990). Of the ten studies that have looked for an association between CT abnormalities and a history of obstetric complications, a link has been found in five. This is despite the low rates of obstetric complications in samples examined, which increases the likelihood of a type 2 error. A positive correlation has been reported between obstetric complications and ventricular size (Turner *et al*, 1986; Pearlson *et al*, 1989), frontal-horn area (DeLisi *et al*, 1986) and combinations of ventricular enlargement with sulcal (Owen *et al*, 1988) or third-ventricle widening (Cannon *et al*, 1989). Five studies have shown no such correlation (Reveley *et al*, 1984; Pearlson *et al*, 1985; Nimgaonkar *et al*, 1988; Johnstone *et al*, 1989; Kaiya *et al*, 1989). The study of Reveley *et al* (1984) found a highly significant association between a reported history of obstetric complications and ventricular size in their healthy control twins, but not in the schizophrenic twins. Curiously, Kaiya *et al* (1989) reported a negative correlation between obstetric complications and ventricular size, although this study also found a negative correlation between ventricular size and length of illness.

Other intriguing associations concerning aetiological factors have emerged in a small number of reports. Increased ventricular size has been found in winter-born schizophrenic patients in at least one study (Zipursky & Schulz, 1987), although has not been shown in others (Dagreef *et al* 1988; Pearlson *et al*, 1989). Two groups have found ventricular enlargement to be significantly associated with left-handedness in schizophrenia (Katsaris & Iacono, 1989; Pearlson *et al*, 1989).

Some conclusions

The story of X-ray CT in schizophrenia research is at the same time enlightening and salutary. As a technique, its inception coincided with the renaissance of biological psychiatry in the 1970s and a torrent of early studies were more or less agreed that ventricular enlargement characterised a large proportion of patients with schizophrenia. More recently, there have been several large, properly controlled studies which have signalled caution about the initial enthusiasm. It is still fair to conclude that relative enlargement of third and lateral ventricles, and cortical sulci, is found in some schizophrenic patients, but the extent of these changes is probably not as marked as first thought. The failure of several rigorous studies to demonstrate these changes has yet to be explained. Variations in sampling methods of patients seems increasingly to be an important factor when appropriate control groups are used. What factors determine the various structural brain parameters in the general population remains an under-researched area and it is becoming obvious that a range of interacting demographic factors such as age, sex, socio-economic status, race, educational level, and alcohol consumption are important. A further caveat is that lateral ventricular enlargement has also been reported in controlled studies of severe affective disorders (see Andreasen *et al*, 1990, for review), and the specificity of these changes to schizophrenia, or to psychosis in general, remains to be shown conclusively. In the light of this, it is perhaps not surprising that the search for clinical correlates of CT changes in schizophrenia has been disappointing, although a relationship with tardive dyskinesia and neuropsychological impairments does seem to exist. One important consequence of this research has been the reappraisal of the natural history of CT abnormalities, where they exist, with the emergence of the view that these are long-standing, non-progressive changes, similar to those seen in other neurodevelopmental disorders (Weinberger, 1987; Murray & Lewis, 1987).

As for the future, although CT will continue to have a role in the testing of specific hypotheses, the baton has now been passed to magnetic resonance imaging as the definitive *in-vivo* structural brain-imaging technique. MRI has the advantages of not using ionising radiation, and its high resolution, good tissue contrast and multiplanar abilities make it the technique of choice in looking at medial brain structures. The use of structural brain imaging in conjunction with techniques such as single-photon or positron-emission CT to visualise regional brain function will be increasingly important, allowing us not just to see the machine, but its ghost as well.

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British Journal of Psychiatry (1990), **157** (suppl. 9)

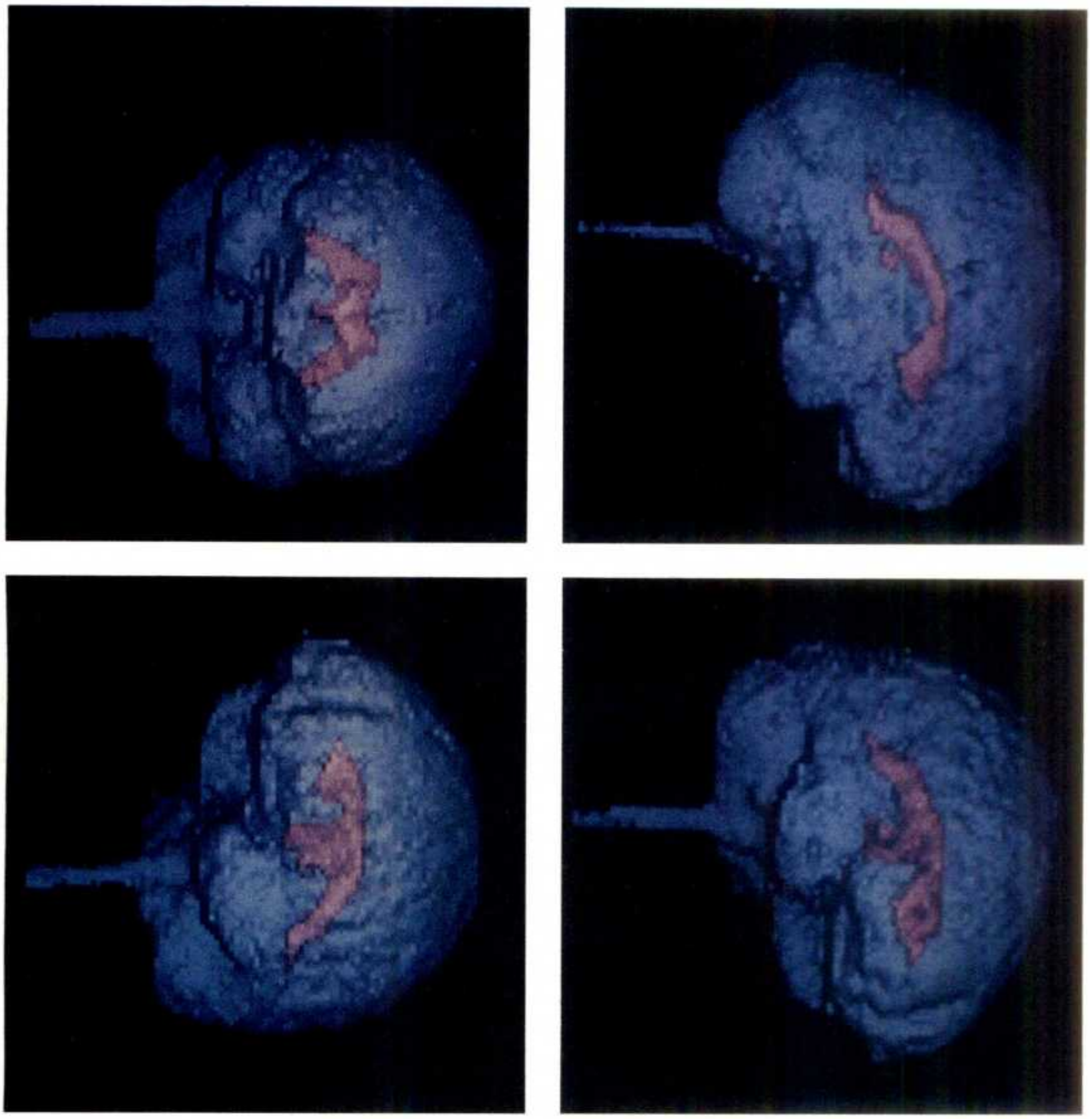
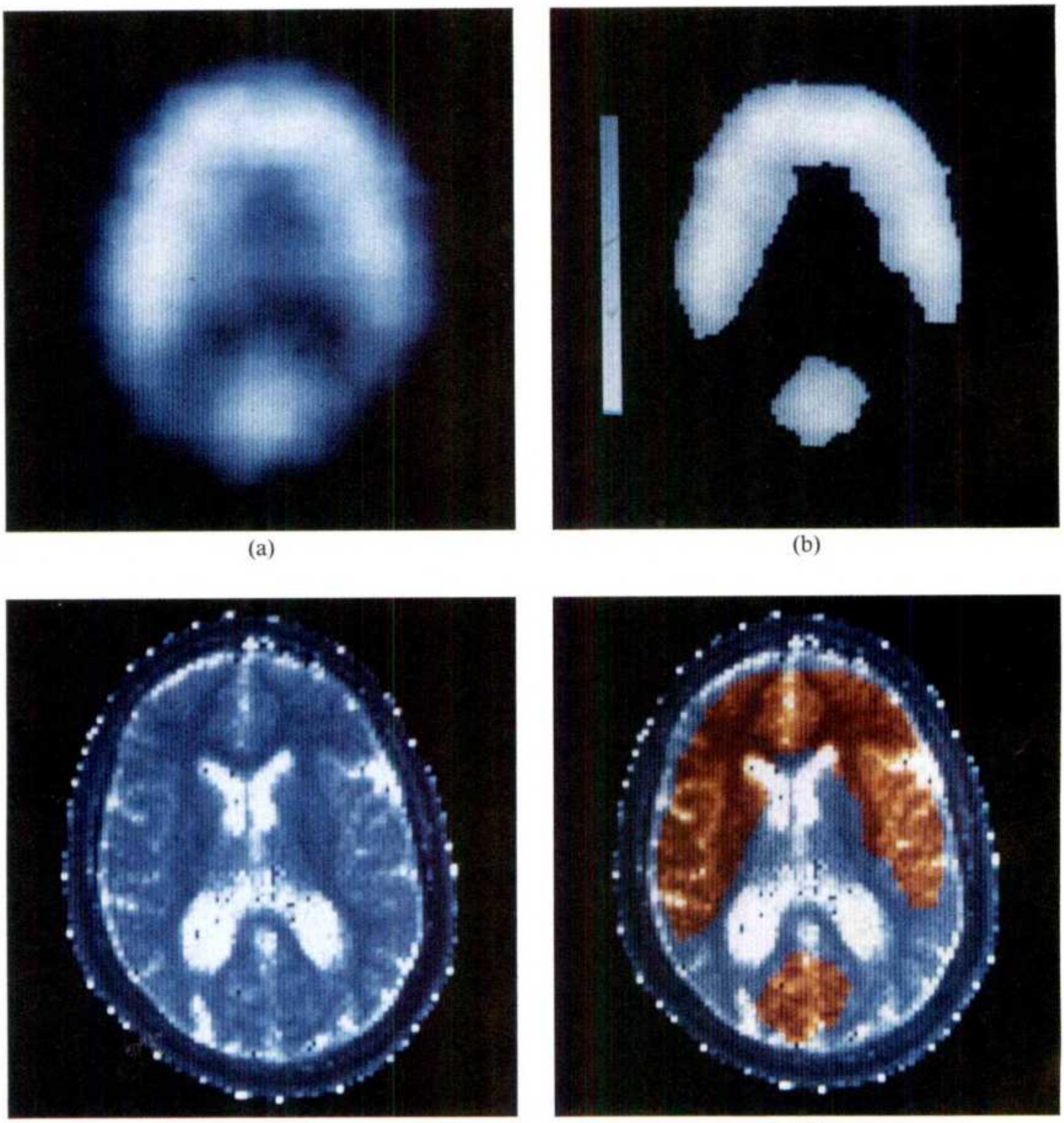


PLATE I (Besson) Whole-brain three-dimensional display with outline of the ventricular system. The imaged structure can be rotated so that it can be viewed from any angle.

British Journal of Psychiatry (1990), **157** (suppl. 9)



(a) (b)

(c) (d)

PLATE II (Besson) Stages of the superimposition of a SPECT cerebral blood-flow image (a), which has been redefined (b), and a MRI T_1-weighted image (c), to produce a combination (d).

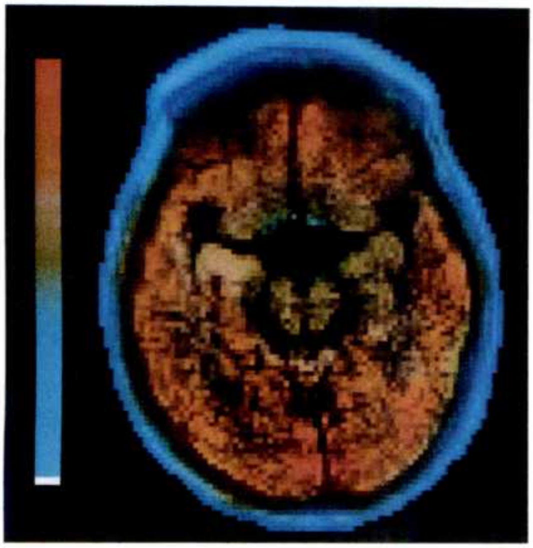


PLATE III (Besson) Superimposed MRI T_1-weighted image and PET image (using ^{18}F-labelled deoxyglucose) of a patient with psychotic depression. The section, taken at the level of the temporal lobe, shows metabolic asymmetry of the amygdaloid nucleus and parahippocampal gyrus.

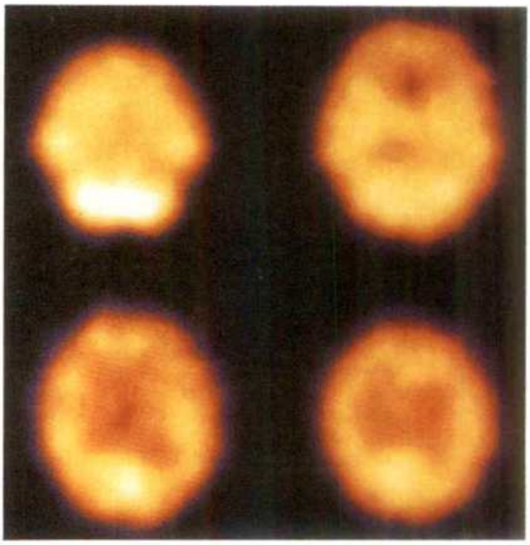
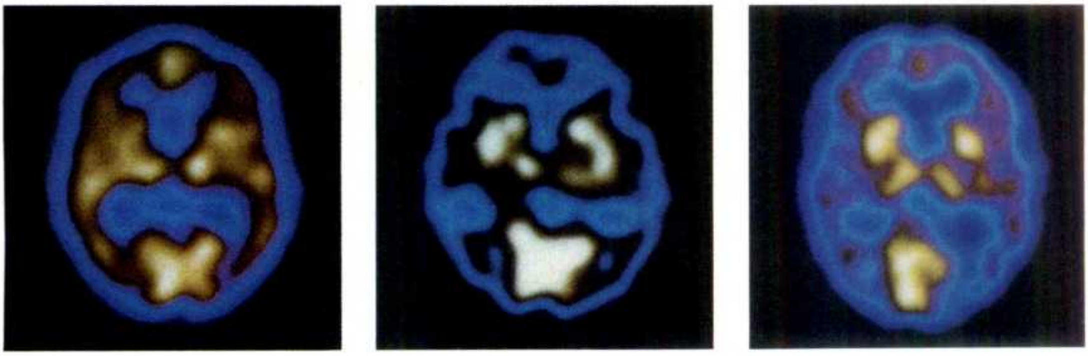
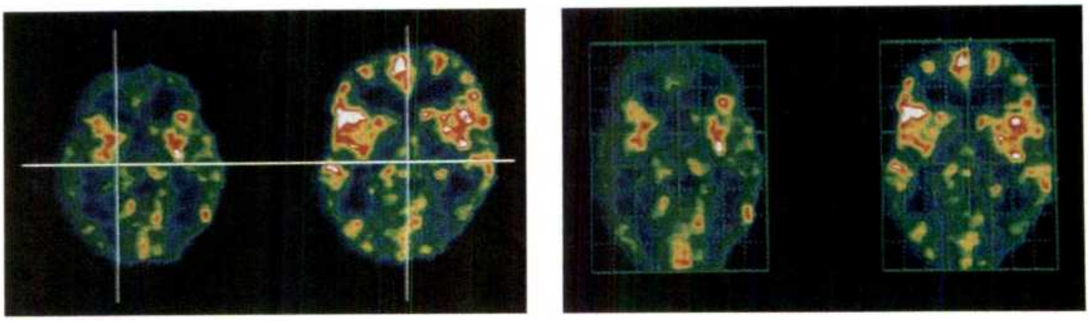


PLATE V (Upadhyaya *et al*) A set of SPECT scans of a depressed patient, showing impaired cerebral perfusion.



(a) (b) (c)

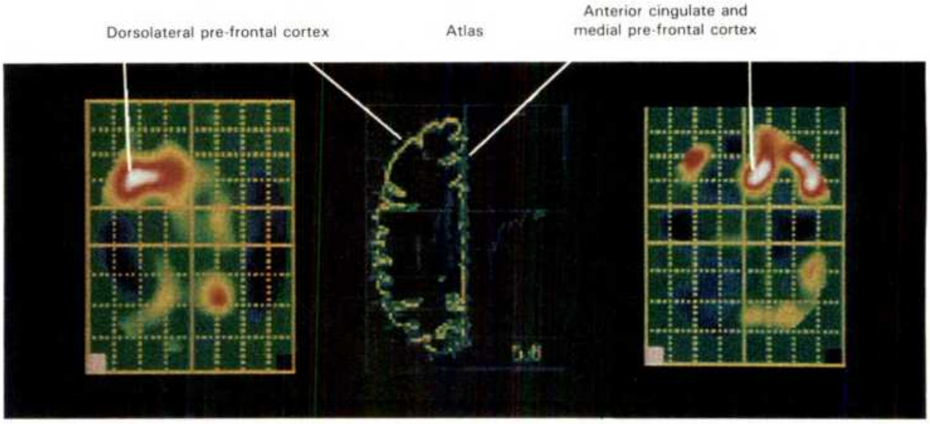
PLATE IV (Geaney & Abou-Saleh) Scans produced by SPECT imaging of ^{99}Tc^{m}-labelled HMPAO: (a) an elderly normal volunteer, (b) a patient with dementia of the Alzheimer type, and (c) a patient with multi-infarct dementia.



Before elastic transformation

After elastic transformation

PLATE VI (Bench *et al*) The effects of non-linear transformation on slices from two different brains of schizophrenic subjects. The grid corresponds to that used by Talairach *et al* (1988). Note the gross non-linear asymmetries before transformation.


Dorsolateral pre-frontal cortex
Atlas
Anterior cingulate and medial pre-frontal cortex
5.6

Verbal fluency

Random movement

PLATE VII (Bench *et al*) Statistical parametric maps (SPMs) of focal activations observed when comparing brain states which involve intrinsic generation of words during a series of verbal-fluency activations (left), and during the generation of random finger movements (right). White areas are t values at $P<0.001$ (not Bonferroni corrected). The grid corresponds to that used by Talairach *et al* (1988). Note that lateral pre-frontal cortices are primarily involved in verbal fluency and medial cortices in random generation.

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Magnetic Resonance Imaging and Its Applications in Neuropsychiatry

J. A. O. BESSON

Theory and applications

The ability to measure the behaviour of protons when influenced by a magnetic field has been known to scientists since the early work of Purcell *et al* (1946) and Bloch (1946). The application of this technique to man, with the ability to reconstruct the data to create an image, is however a more recent innovation. Early work in this area was carried out by Damadian (1977) and Lautebur (1979) in New York, Mansfield & Maudsley (1977) in Nottingham, and Mallard *et al* (1979) in Aberdeen. The general principles of all these systems are similar, although the technical approaches have differed.

The most common nucleus in biological tissue is the hydrogen nucleus, or proton. Protons spin, and the alignment of this spin is random. However, if the spinning protons are placed in a static magnetic field, they align themselves in the direction of that magnetic field. The axis of the spin is not absolutely parallel to the direction of this external magnetic field, but circles or precesses a few degrees off that axis. The rate of precession is called the Lamour frequency. The Lamour frequency (w) can be calculated from the equation $w=\gamma\times B$, where γ refers to the gyromagnetic ratio (a constant) and B is the strength of the magnetic field. The gyromagnetic ratio is constant for each particular type of nucleus. Only nuclei that have certain gyromagnetic characteristics can be influenced by a magnetic field. Those of medical relevance are ^{13}C, ^{31}P, ^{23}Na, ^{19}F, ^{17}O, and ^{15}N.

Placing the protons in a static magnetic field aligns them in the direction of that magnetic field and creates a small magnetic moment pointing in that direction. In order to measure that net magnetic moment, a radiofrequency pulse is administered which transiently alters the direction of the net magnetic moment by 90°. In doing so energy is taken into the system then subsequently dissipated. This energy is provided by the radiofrequency pulse and the frequency of this pulse has to be the same as the frequency at which the protons are precessing. After the radiofrequency pulse has been removed the protons return to their previous spin direction, emitting energy as they do so; the rate at which this energy signal decays is referred to as the relaxation time. The differing relaxation times between tissues confer contrast between these tissues on the image. The image is composed of a number of small cubes or voxels (volume elements) corresponding to small volumes of brain tissue of a given mean value of relaxation time. These may be displayed on either a colour scale or a grey scale, with each colour or shade representing a relaxation time.

During magnetic resonance imaging (MRI), three components of the signal are utilised. These are the proton density, the spin-lattice relaxation time or longitudinal relaxation time (T_1) and the spin-spin relaxation time or transverse relaxation time (T_2).

The proton density represents the number of protons present in the tissue. The pulse sequence used to produce proton-density images is called the saturation-recovery (SR) component. These are obtained following the application of the 90° radiofrequency pulse. Proton-density images demonstrate little contrast between soft tissues, for example, between grey matter and white matter. They do however show good contrast between soft tissues and cerebrospinal fluid (CSF), and as such outline the ventricular system and the grey-matter-CSF interface with precision.

The T_1 relaxation time represents the return of the proton magnetic moment to its previous equilibrium state in line with the axis of magnetisation conveyed by the static magnetic field. T_1 is defined as the time required for the net magnetisation following radiofrequency excitation to return to 63% of its original value. The relaxation process decays exponentially with time and is different for different tissues, thus giving differentiation between or characterisation of tissues, including normal tissue and pathological states.

The proton concentration and composition varies within tissues and varies within pathology and thus the rate of relaxation varies. With respect to brain, relaxation times are longest in CSF, shorter in grey matter, and shorter still in white matter. In most pathological conditions, relaxation times are longer than in the normal tissue. The actual values for relaxation times vary with the field strength of the magnet used in the imaging process. Systems of low field strength give greater sensitivity to change in relaxation times and thus can identify smaller changes in T_1 measurements in tissues but have the disadvantage of giving poorer resolution to the image because of the greater voxel size.

The T_2 relaxation time results from the interaction of the spinning proton following 90° excitation with the spins of other nuclei. This interaction results in a 'dephasing' of the spins and causes loss of signal strength. In this process of dephasing, the precession of the nuclei lose their synchronicity and instead of spinning in the same manner, some spin more rapidly and some spin more slowly than others. As the proton spin returns to its original axis, so the amplitude of the signal which occurs as a result of the dephasing of the spins decays exponentially to zero. T_2 is defined as the time required for the signal to return to 37% of its original value. Like T_1, T_2 varies with different tissues and with pathology and is also influenced by the field strength of the magnet used in the imaging process.

There are three types of pulse sequence applied in order to obtain images. These are saturation–recovery, inversion–recovery and spin–echo. Saturation–recovery images rely entirely on proton density and as such discriminate poorly between different types of tissue. Inversion–recovery sequences involve the application of two radiofrequency signals. First a 180° pulse excites the protons and aligns them at 180° to the original direction (hence the term 'inversion') and after this the magnetic moment relaxes and realigns itself to its former level. However, in order to measure the decay characteristic of the relaxation, it is necessary to use a second radiofrequency pulse at 90° to the original alignment. The time interval between the 180° pulse and the 90° pulse is called the inversion time (TI) and this time may be varied. Varying the TI would result in different degrees of contrast in the image and may be useful for defining certain specific pathologies, but optimum levels can be selected specifically for each image for general or routine use. Because this pulse sequence is heavily influenced by the T_1 component of the MR signal it is often described as being T_1-weighted. Inversion–recovery pulse sequences are very good for distinguishing between grey and white matter and therefore produce high-quality anatomical displays.

In the spin–echo sequence, the 90° radiofrequency pulse is first administered and alters the direction of the magnetic moment 90° to its original axis. Dephasing of the spins occurs and this is influenced by inhomogeneities in the magnetic field, giving rise to artefacts. The spin–echo sequence is designed to reduce these artefacts. At a given time interval after the 90° pulse a 180° pulse is applied. This alters the direction of the magnetic moment 180°. The interval between the 90° and 180° pulse is referred to as tau and at a time of twice the tau a measurement of signal is obtained. This time interval is referred to as the time to echo (TE). The whole process is then repeated and the total time between the repetition of the whole pulse sequence is referred to as repetition time (TR). Generally speaking, spin–echo sequences produce images of poorer anatomical quality but are sensitive for detecting pathological lesions. Because spin–echo images rely mainly on the T_2 component of the MR signal, they are referred to as T_2-weighted images. Again, as in inversion–recovery, the time intervals TE and TR can be manipulated to define more clearly specific characteristics of the image.

In order to permit anatomical localisation of various signal voxels within the mass of tissue being imaged, gradient magnets are used. Resonating nuclei within each voxel are selectively activated in adjacent parts of the brain independently, thus producing a spatial organisation of the signals in a three-dimensional manner that can then be reconstructed using the computer, to create transverse sagittal or coronal displays or, more recently, three-dimensional displays which can then be sectioned to illustrate the desired structure. Plate I shows the whole brain, with outlining of the ventricular system; this image can be displayed at any angle on the video display unit.

Magnetic resonance imaging systems have been available since about 1980. The earlier systems tended to be of lower field strength and to use resistive magnets. More recently superconducting magnets of higher field strength are now more readily available and have the capacity to image in at least three planes with a multislice facility, providing a mixture of inversion–recovery and spin–echo pulse sequences with the capacity to vary TI, TE and TR and also to vary the thickness of each slice. In addition to this, because MRI does not employ ionising radiation, it may be safely used on the same patient for several imaging sessions and thus is well suited for longitudinal studies of disease states. It is more sensitive than X-ray computerised tomography (CT) for identifying cerebral tumours, demyelination and other pathologies but is less sensitive for detecting calcification. In addition to this, the presence of metallic objects will make a hole within the image and similarly surgical clips that have a ferromagnetic component may potentially be dislodged by strong magnetic fields. The fact that cortical bone has low proton density means that obscuring certain regions of the brain, for example posterior fossa, is much less likely to occur than

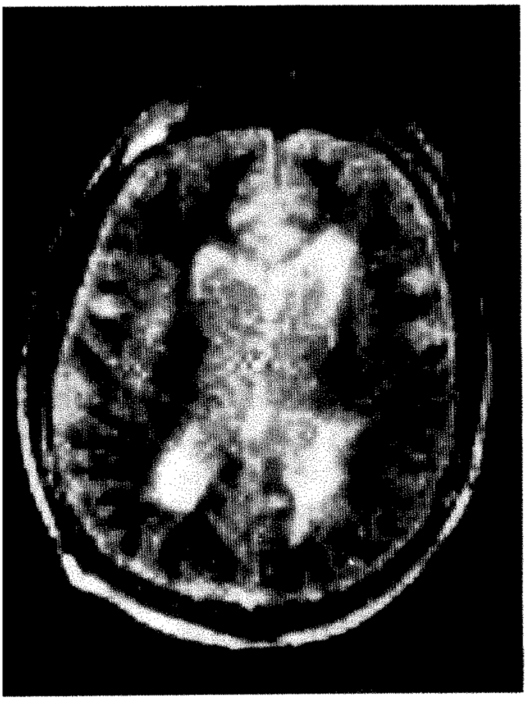
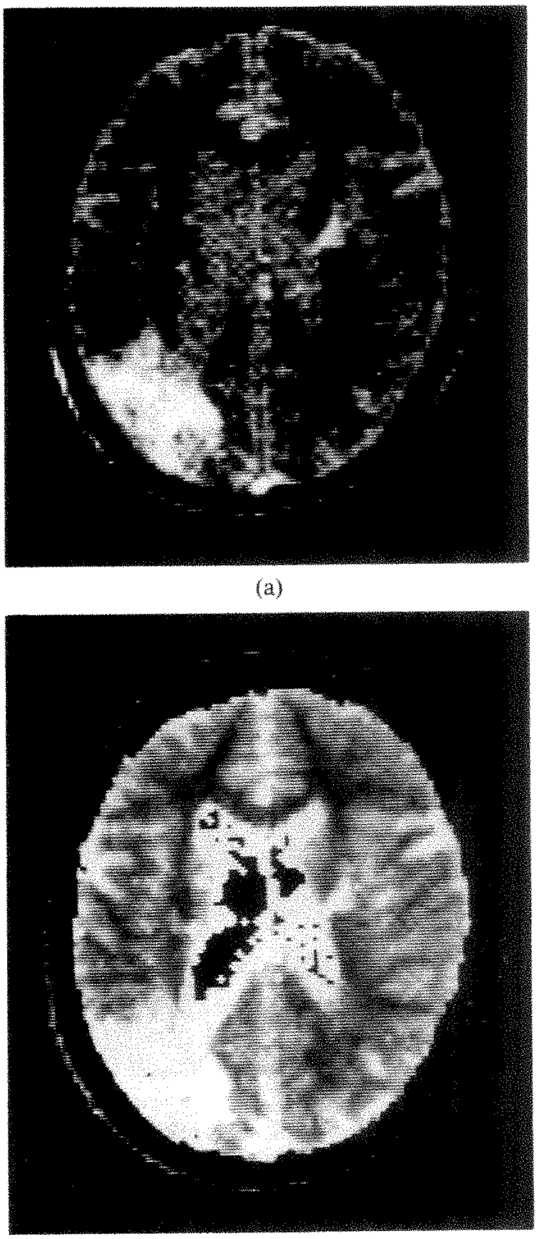


FIG. 1 Inversion-recovery image of a patient with multiple sclerosis showing changes to the periventricular white matter.

is the case with X-ray CT. Patients with cardiac pacemakers cannot be imaged and those who are claustrophobic may find the procedure distressing.

The detection of lesions in neuropsychiatric disorders

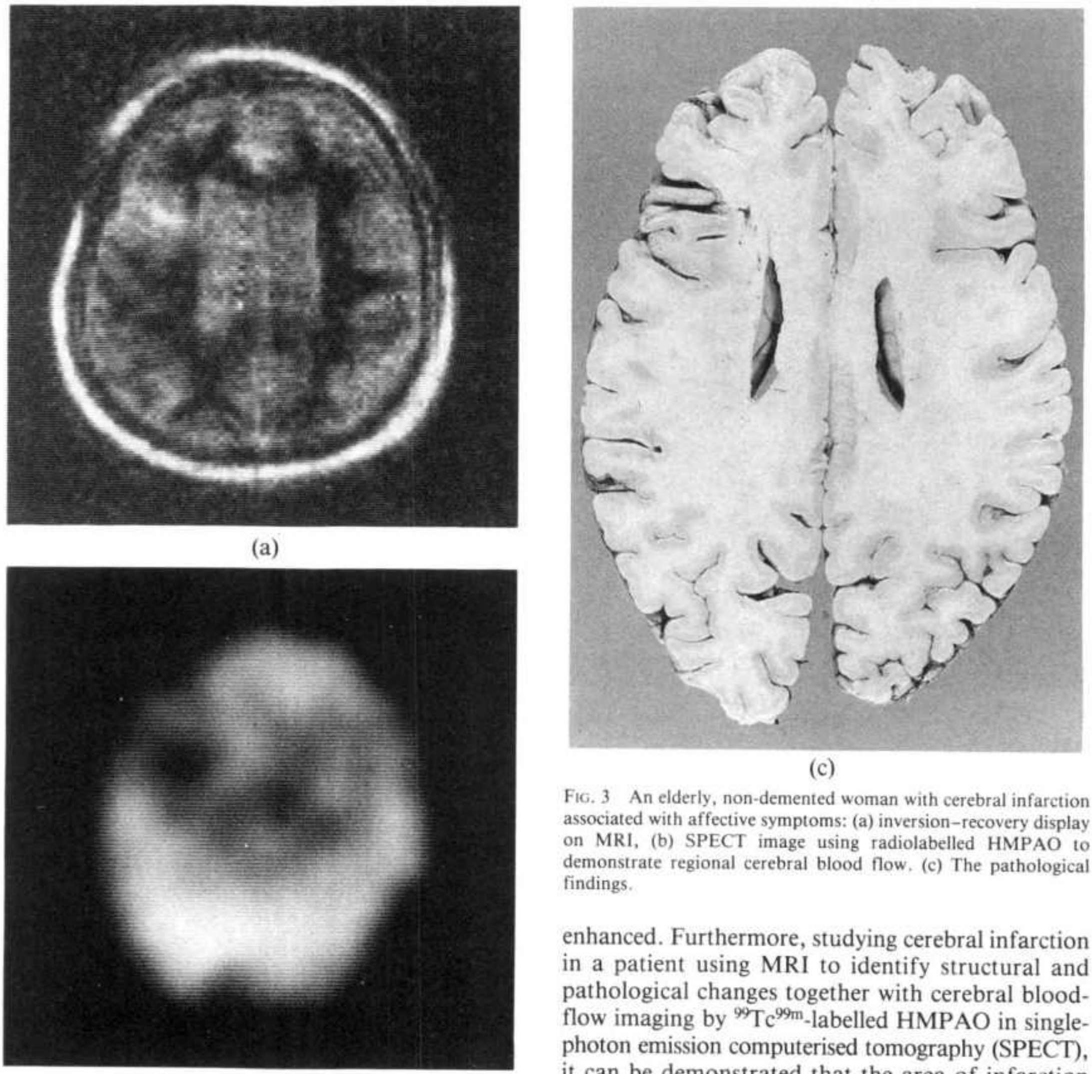
Magnetic resonance imaging may be useful in the study of patients who present with psychiatric symptoms as a feature of neurological disease. The most well studied example of this is multiple sclerosis: white-matter lesions are well identified as areas of increased signal intensity. Figure 1 shows these in the periventricular regions. Several studies have indicated that these are identified more sensitively by MRI than by X-ray CT, particularly in the brain-stem (Young *et al*, 1981), and MRI is believed to detect some asymptomatic lesions (Paty *et al*, 1988). Rao *et al* (1989) demonstrated that in patients with multiple sclerosis there was a strong relationship between severity of cerebral pathology on MRI and cognitive impairment. In patients with isolated lesions of the type seen in multiple sclerosis, tests of auditory attention and abstracting ability correlated with total lesion score – a value reflecting the size and number of lesions in a combination of the periventricular areas, internal capsule, basal ganglia, and frontal parietal temporal and occipital lobes. However, significant correlations were not present between cognitive test scores and regional scores on MRI of



(a)

(b)

FIG. 2 Cerebral infarction demonstrated by MRI scans: (a) inversion-recovery image, (b) T_1 image.



(a)

(b)

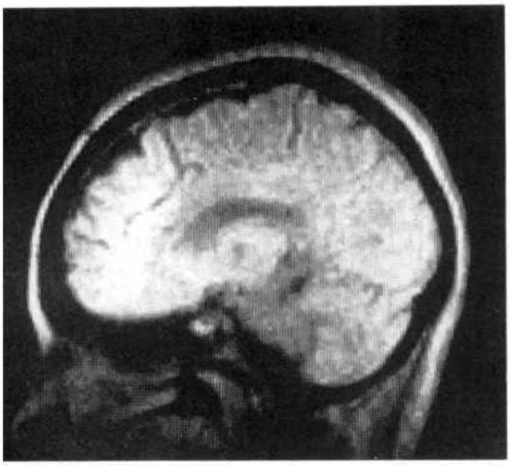
(c)

FIG. 3 An elderly, non-demented woman with cerebral infarction associated with affective symptoms: (a) inversion–recovery display on MRI, (b) SPECT image using radiolabelled HMPAO to demonstrate regional cerebral blood flow. (c) The pathological findings.

the periventricular frontal and temporal areas. Those patients with the greatest lesion scores showed greatest cognitive decline (Callanan *et al*, 1989). Anzola *et al* (1990) found that the presence of extensive periventricular demyelination was associated with a subcortical profile of cognitive impairment in patients with a relapsing–remitting pattern of disease and mild cognitive impairment.

Infarcts can be characterised by their relaxation-time characteristics and staged in terms of age and type (Fig. 2). Besson (1987) indicated that by studying lesion characteristics in images taken in several modalities, the diagnostic precision in ageing and categorising lesions, especially infarcts, can be enhanced. Furthermore, studying cerebral infarction in a patient using MRI to identify structural and pathological changes together with cerebral blood-flow imaging by ^{99}Tc^{99m}-labelled HMPAO in single-photon emission computerised tomography (SPECT), it can be demonstrated that the area of infarction demonstrated on MRI and confirmed on subsequent pathology is much smaller than the area of reduced perfusion as imaged by SPECT. This is illustrated in Fig. 3; the patient, an elderly woman, did not suffer from dementia but had a clinical presentation of chronic hypomania of late onset, responding only partially to neuroleptics or lithium but improving with carbarmazepine.

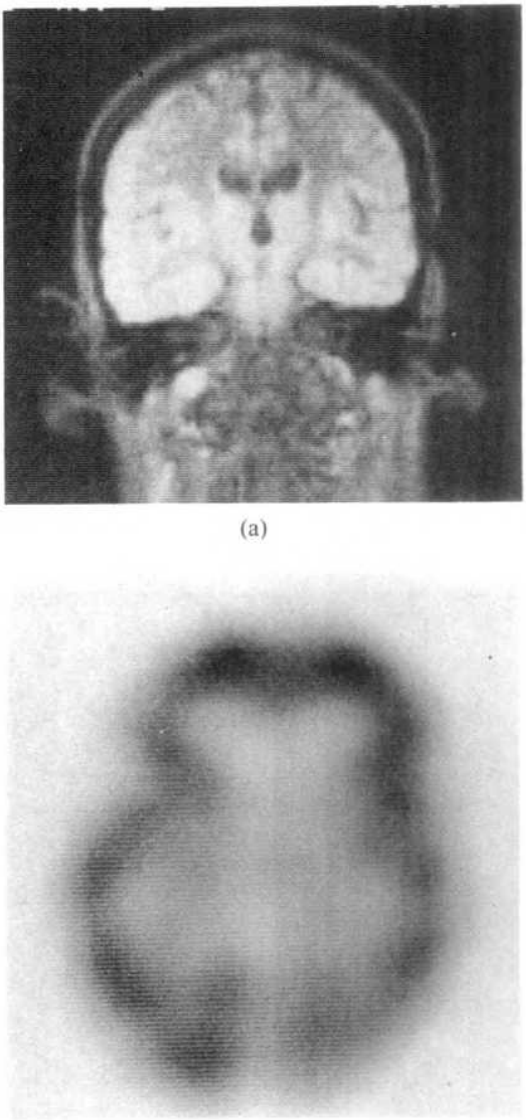
The ability to image patients in sagittal, coronal and transverse planes also provides the opportunity to enhance the detection of certain lesions. Figure 4 shows the parasagittal image of a 35-year-old patient who presented with a dysmnesic syndrome and mood disorder. X-ray CT was entirely normal but the parasagittal display on MRI showed a small thalamic infarct.



IG. 4 Parasagittal section on MRI of the brain of a 35-year-old atient with a small thalamic infarct, which had produced a ysmnesic syndrome and mood disorder.

Coronal images enhance the display of the basal anglia and their connections to the cerebellum via the rain-stem. This projection is displayed in Figure 5(a). 20-year-old woman with Wilson's disease presented ith emotional lability, inappropriate affect, histrionic behaviour', and dystonic moments of the rms; MRI showed increased T_1 values in the basal anglia compared with that of normal subjects. ollowing treatment with penicillamine for one year, here was virtually complete remission in clinical ymptoms and signs and a T_1 fall of the basal anglia amounting to 70% of the increase above ormal values. It should be noted that a cereral SPECT scan (Fig. 5(b)) showed marked eduction generally in basal ganglia uptake of the racer.

There are some situations in which MRI does ot have demonstrable advantage over X-ray CT. ntracerebral calcification is an example of this. igure 6(a) shows the X-ray CT of a patient ith Fahr's syndrome – familial calcification of he basal ganglia. This patient presented with a chizophreniform psychosis and dementia with nset in adolescence. X-ray of the head and -ray CT of the brain demonstrated calcification f the basal ganglia. His mother showed the ame characteristics but was asymptomatic from psychiatric point of view and his brother, ndoubtedly eccentric, never declaring symptoms, nd ultimately committing suicide, had a similar bnormality. MRI was normal, as was the SPECT can (Fig 6 (b, c)).



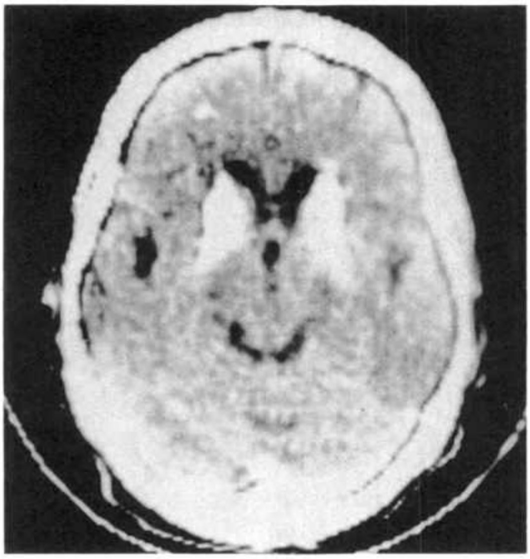
(a)

(b)

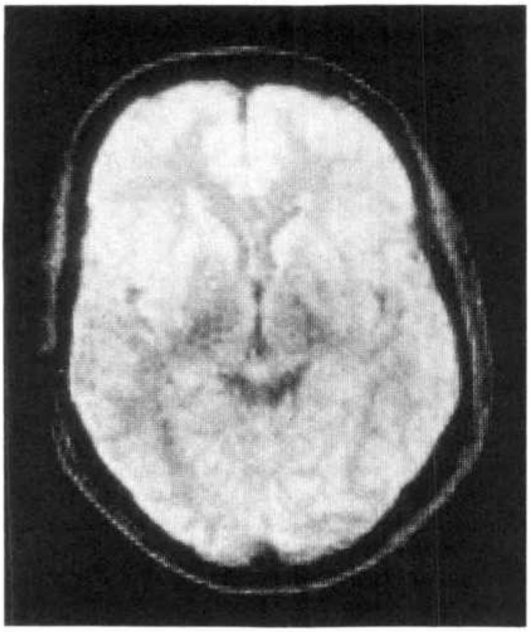
FIG. 5 Images of a patient with Wilson's disease: (a) MRI coronal view showing enhanced signal in basal ganglia, (b) cerebral blood-flow (SPECT) image showing reduced basal ganglia activity.

Multimodality imaging

The previous section has indicated that imaging the same patient to identify structural change with MRI and regional function by blood flow, for example, can enhance the ability to determine the nature and functional changes within regions. Displays of



(a)



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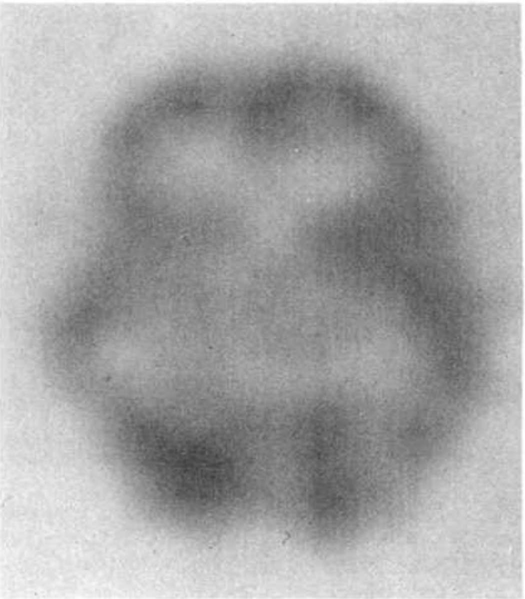

(c)

FIG. 6 (a) A CT scan showing calcification of basal ganglia in Fahr's syndrome. (b) MRI is able to show only minimal change in basal ganglia. (c) A SPECT scan using radiolabelled HMPAO shows normal blood flow in the basal ganglia.

images which identify structure (e.g. MRI) and function (e.g. cerebral blood flow using SPECT, or glucose metabolism using positron-emission tomography (PET)) may be examined separately or may be superimposed one on the other (Wells *et al*, 1989). To do this effectively, the images taken in the modalities to be superimposed must be precisely aligned, and several techniques involving stereotaxic frame positioning of the patient or using common-modality external markers (those capable of being detected by both X-ray (e.g. lead) and magnetic (e.g. copper sulphate solution) techniques). Images obtained by different modalities are often of different dimensions, and therefore rescaling of the subsequent display is necessary. These techniques require quite complex computing manoeuvres in order to achieve the desired precision.

Plate II shows (a) a SPECT cerebral blood-flow image of a patient with bilateral posterior parietal perfusion deficits often seen in Alzheimer's disease, and (c) a T_1 image taken at the same level. By enhancing the contrast of the cerebral blood-flow image (b), greater definition is achieved, and after converting this to a colour-display format, it is superimposed on the T_1 image (d).

A similar process can be applied to ^{18}F-labelled deoxyglucose and PET images. Plate III shows the superimposed MRI and a PET image using ^{18}F-labelled deoxyglucose, from a patient with psychotic depression. The structural aspects of the image are conferred by the MRI component and show the temporal lobe with the amygdaloid nuclei, parahippocampal gyrus and hippocampus and the orbital surface of the frontal lobe. The functional component of the image obtained by PET and displayed by a colour scale shows asymmetric metabolic activity in the amygdaloid nucleus and other medial temporal structures. The precise anatomical delineation would not have been apparent had superimposition on an anatomical image not been carried out.

Quantitative applications of MRI

Magnetic resonance imaging may be used to measure the size of brain compartments in order to determine either the presence of general atrophy of the whole brain or regional atrophy in specific areas of the brain by measuring linear or area ratios in the same manner as for X-ray CT studies. The real advantage over X-ray CT, however, is the ability to measure the volume of brain structures using computerised three-dimensional reconstruction of the images. These techniques have the advantages of allowing more subtle discrimination and can be used to separate some of the changes due to ageing from those due to atrophic processes and pathology.

An example of this is the demonstration by Seab *et al* (1988) that the hippocampal volume in Alzheimer's disease, normalised relative to the size of the lenticular nucleus (spared in Alzheimer's disease), was reduced by 40% compared with that in matched controls, with no overlap between the two groups. Overall measures of brain atrophy (ventricular and sulcal enlargement) showed significantly different group means but overlap did occur between subjects in the two groups. Hippocampal atrophy did not correlate with either overall brain atrophy or the severity of dementia, although the degree of overall atrophy does correlate with severity of dementia. This study demonstrated *in vivo* that hippocampal atrophy occurs early in Alzheimer's disease and may be a more sensitive detector of the disease than other measurements of ventricular size, sulcal enlargement, or overall brain atrophy. This is in keeping with the observation of pathological studies that the earliest and most severely involved areas of the brain are in the median limbic and temporal basal grey-matter structures which include the hippocampus. However, brain atrophy appears to be a better index of disease severity, suggesting that the symptoms that arise as the disease progresses are predominantly cortically determined.

Attempts to measure atrophy and to distinguish primary degenerative atrophy from that resulting from increased CSF pressure have been carried out by measuring the intracranial extraventricular and ventricular CSF volumes (Condon *et al*, 1986). These studies used sagittal displays of images and measured the volume of pixels that had a relaxation time the same as that of water imaged in a phial simultaneously with the imaging of the patient. The volume of the CSF was then measured in the ventricles and in the subarachnoid space and was shown to distinguish between cerebral atrophy, especially that due to Alzheimer's disease, and adult obstructive hydrocephalus and also benign intracranial hypertension.

Pathological correlates of MRI findings

Magnetic resonance imaging can also be used to identify regions of focal pathology, owing to their altered relaxation times. When these alterations are gross, lesions can be seen and the determination of their pathology may be assisted by morphological characteristics and intensity of changes visualised within the image. Several studies have now clearly demonstrated that white-matter lesions due to demyelination in patients with multiple sclerosis are much more readily detected by MRI than by X-ray CT. Furthermore, it is possible to distinguish between infarcts (both recent and established), tumours and ischaemic areas on the basis of their differential effects on image intensity in the various modes of display that are possible.

White-matter lesions for example have been observed in patients with Alzheimer's disease, multi-infarct dementia, and in some elderly non-demented subjects – Gerard & Weisberg (1986) have shown that as many as 30% of normal healthy subjects over the age of 60 have periventricular white-matter change. Post-mortem imaging of the brain with subsequent pathological and histological examination demonstrated that when smooth lesions of high signal intensity appeared in the anterior horn, this was not associated with abnormalities of pathology of brain parenchyma, whereas those lesions that had a lumpy appearance are more indicative of pathology (Grant *et al*, 1987).

Scanning of formalin-fixed post-mortem brain has shown that regions of abnormal MRI signal in multiple sclerosis corresponded to plaques seen histologically, and that lesions as small as 3 mm in diameter can be detected (Stewart *et al*, 1984). A similar study carried out on patients with subcortical arteriosclerotic encephalopathy or Binswanger's disease, using brains that had been fixed in formalin for 1–12 years and which were subjected to pathological examination after imaging, showed good correlation between the extent and severity of the abnormal MRI signal and the pathological changes (Revesz *et al*, 1989). Areas of diffuse MRI abnormality corresponded to areas of axonal and myelin loss with gliosis, and small lacuna-like lesions on

MRI corresponded to lacuna infarcts histologically. It was concluded that the abnormal signal probably emanates from increased tissue water attributable to gliosis and an expanded extracellular space, although in these cases absolute measures of relaxation time or the water content of the tissue were not determined. Imaging animals with artificially induced experimental oedematous or gliotic lesions have shown differential changes in relaxation times between T_1 and T_2, with different magnetisation decay characteristics (Barnes *et al*, 1987, 1988). These differences may provide a model of distinguishing on MRI between lesions of differing pathologies in man.

There is considerable debate as to the nature and diagnostic significance of white-matter lesions in normal elderly controls, those with Alzheimer's disease and those with multi-infarct dementia (MID). Using clinical diagnostic criteria to distinguish Alzheimer's from MID, Ebmeier *et al* (1987) demonstrated that periventricular change (high signal intensity) was found in both Alzheimer's disease and MID and therefore was not of diagnostic significance, but that clinical diagnosis of MID correlated most highly with the presence of infarcts. Besson *et al* (1985) demonstrated that T_1 values were increased in elderly patients with Alzheimer's disease, and the increase correlated with the severity of dementia and was particularly focused in the temporal parietal region. Similar findings were demonstrated with respect to T_2 by Bondareff *et al* (1988). Furthermore, Bondareff *et al* (1990) demonstrated that the amount of white-matter lesions, after controlling for brain size, correlated with dementia scores as measured by the Blessed Dementia Scale and Folstein Mini Mental State Examination. Christie *et al* (1988), however, were unable to show increased T_1 in pre-senile cases of Alzheimer's disease.

Englund *et al* (1987) measured post-mortem T_1, T_2 and water content of brain regions of patients with Alzheimer's disease and demonstrated that T_1, T_2 and water content were increased, and this increase was proportional to the degree of infarction identified by histopathological examination. Old complete infarcts had the longest relaxation times while incomplete white-matter infarcts had less prolonged relaxation times. Incomplete white-matter infarcts were characterised by partial loss of myelin, axons and oligodendroglial cells, mild reactive astrocytic gliosis, and sparsely distributed macrophages. In addition arteriolar stenosis resulting from hyaline fibrosis was present. These were confined to the white matter and lacked the components of a complete infarct. It was speculated by Brun & Englund (1986*a*) that these changes were due to regional hypoperfusion and they were called 'selected incomplete white-matter infarctions'. Histologically they were said to be similar to incomplete white-matter infarction in the zone encircling old white-matter infarcts. Biochemical examination of these areas (Englund *et al*, 1988) has shown that the greater the ischaemic pathology identified by the histological criteria laid by Brun & Englund (1986*b*), the greater the reduction in several biochemical components. The total protein content, for example, of the samples was reduced, and this was proportional to the greater degree of incomplete white-matter change. Similar trends of reductions are seen in phospholipid content, cholesterol, cerebrosides and sulphatides. Water content, however, progressively increased.

Thus it would seem that in Alzheimer's disease there is increased T_1 and T_2 in white matter measured on the images *in vivo*. Furthermore, *in-vitro* measures of T_1 and T_2 support these findings and confirm that they are related to increased water content and probably also to reduced macromolecular content in the form of reduced total protein, phospholipids, cholesterol, cerebrosides and sulphatides.. These findings seem to correspond to histopathological changes whereby there was reduction in the axonal and myelin component in the context of fibrous sclerosis of the arterioles. While this explanation relating relaxation times, water content and macromolecular structures together with rarefaction of myelin-staining elements within the tissue seems reasonable, the question emerges as to the pathogenesis of these changes. While the histological evidence for infarction is compelling, the concept of selective, incomplete white-matter infarction as a pathological entity is less clear. Indeed, when the same patients with Alzheimer's disease were imaged with MRI and SPECT, and were assessed for cognitive function (in particular for the presence of visuospatial deficits) and were subsequently examined pathologically, it was demonstrated that the marked deficits in temporoparietal flow (previously established as a frequent finding in Alzheimer's disease (Gemmell *et al*, 1987) using this technique) were most pronounced in regions adjacent to areas of greatest white-matter T_1 increase. Furthermore ischaemic changes (infarction, incomplete or otherwise) did not occur in the white-matter areas (Besson *et al*, 1990) (Fig. 7). When grey matter of these patients is examined histologically at post-mortem, the regions of reduced cerebral blood flow on the SPECT images do not show evidence of infarction or ischaemia (Fig. 8). These areas have already been demonstrated to be the most affected in Alzheimer's disease from a pathological point of view, and to demonstrate

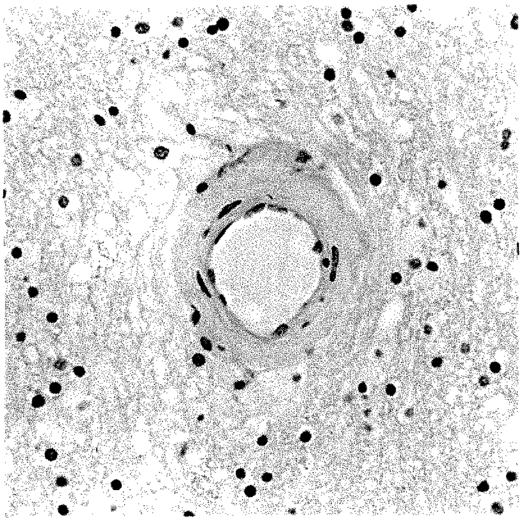

FIG. 7 White matter stained with haematoxylin and eosin of posterior parietal region in a patient with Alzheimer's disease showing increased T_1 in posterior parietal white matter on MRI. This shows hyaline fibrosis of arterioles but no evidence of infarction (complete or incomplete) or of ischaemic change.

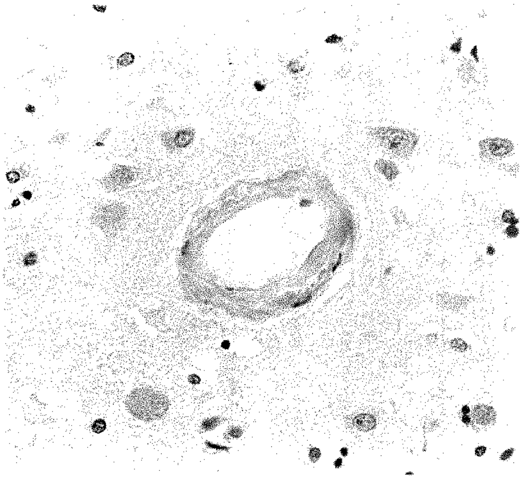

FIG. 8 Grey matter from posterior parietal region of a patient with Alzheimer's disease who had a markedly reduced cerebral blood flow on a SPECT image. This section was stained with congo red and shows perivascular amyloid but no ischaemic change or evidence of infarction.

the greatest regions of functional and structural abnormality using brain-imaging techniques (Brun & Englund, 1986*a*,*b*).

An alternative explanation for these changes is that they reflect white-matter atrophy consequent upon adjacent grey-matter neuronal loss probably resulting from Wallerian degeneration. This explanation is supported by the findings of Ebmeier *et al* (1987) that the characteristics of the white-matter lesions in Alzheimer's disease and MID are different and are reflected by different intensities of T_1 change. Thus it would appear that there might be two types of lesion to be found in white matter. Those related to vascular disturbance are characterised by more compelling histological evidence of infarction, greater intensity of T_1 change on images, and markedly increased T_1 and water content findings, the latter perhaps associated with cystic formation following infarction and representing more clearly vascular lesions. On the other hand there are more subtle changes on the image with relaxation times that are not so markedly elevated, with somewhat greater water content reflecting atrophic change within the axonal elements of the tissue and manifest by rarefaction on myelin staining, and perhaps reflecting degeneration of those cellular elements. These two opposing views require reconciliation.

Multimodel approaches to understanding MRI changes: the case of alcoholic brain disease

Since the first study demonstrating that T_1 is increased in chronic alcoholics during the early withdrawal phase and that this is maintained even after the recovery of the acute phase of the illness, several studies have now been carried out that have substantiated these early findings, despite the fact that initially somewhat controversial results were obtained (Smith *et al*, 1985; Logsdial *et al*, 1987). Table I summarises the findings of T_1 and T_2 changes in response to alcohol administration. Chronic alcoholic patients and rats administered alcohol for six months have increased T_1 in the brain and normal T_2. The red cells of chronic alcoholic patients have increased T_1 and T_2. In the case of brain tissue, the increased T_1 persists even with abstinence (Besson *et al*, 1987; Chick *et al*, 1989) and worsens with continued drinking (Chick *et al*, 1989). Abstinent patients with alcoholic dementia (Besson *et al*, 1990) and with Korsakoff's psychosis (Christie *et al*, 1988; Besson *et al*, 1989*c*) have increased brain T_1. The weight of evidence is thus overwhelmingly in favour of increased relaxation times in chronic dependent individuals or animals with a progression in continued drinking, but with the potential for some reversal – complete in the case of abstinent rats and red blood cells of abstinent

TABLE I

Direction of T_1 and T_2 change following ethanol exposure compared with normal controls

Study	*Tissue type*	*Acute/chronic administration*	*Intoxicated*	*48 hours withdrawal*	*1–4 weeks*	*2 months*	*3 months*	*6 months*
T_1 *change*								
Besson *et al* (1981)	Brain	Chronic	No change		Increase			
Mander *et al* (1985)	Brain	Acute (volunteers)	Decrease					
Smith *et al* (1985)	Brain	Chronic		Increase	No change			
Besson *et al* (1987)	Brain	Chronic			Increase		Increase	
Mander *et al* (1988)	Brain	Chronic		Increase	Increase			
Chick *et al* (1989)	Brain	Chronic			Increase			Increase
Besson *et al* (1989*a*)	Rat Brain	Acute	No change					
Logsdial *et al* (1987)	Brain	Acute (volunteers)	No change					
Besson *et al* (1989*a*)	Rat brain	Dependent	No change	No change				
Besson *et al* (1989*b*, 1990)	Red cells	Chronic			Increase		Increase	No change
Besson *et al* (1989*a*)	Rat brain	Chronic	No change		Increase	No change		
Mander (1989)	Brain	Chronic		Decrease compared with Intoxicated group				
T_2 *change*								
Logsdial *et al* (1987)	Brain	Acute (volunteers)	No change					
Besson *et al* (1989*a*)	Rat brain	Dependent	No change	No change				
Besson *et al* (1989*b*, 1990)	Red cells	Chronic			Increase	Increase	No change	No change
Besson *et al* (1989*a*)	Rat brain	Chronic	No change		No change	No change		

TABLE II

Ethanol-induced changes in phospholipid fatty acid composition[1] in rats withdrawing and recovered from alcohol addiction

	Cortex			Mid-brain		
Fatty acid	*Control*	*Withdrawing*	*Recovered*	*Control*	*Withdrawing*	*Recovered*
Phosphatidylcholine						
16:0	44.2 (1.2)	43.0 (0.5)	44.6 (2.6)	36.8 (0.7)	36.9 (1.7)	38.4 (1.1)
18:0	12.4 (0.4)	13.0 (0.2)	15.3 (1.8)	15.7 (0.1)	15.3 (0.4)	14.6 (0.4)
18:1	28.8 (0.7)	29.8 (0.4)	25.0 (3.6)	35.0 (0.9)	35.4 (0.6)	34.6 (0.6)
20:4	6.5 (0.5)	6.1 (0.2)	5.3 (0.7)	4.0 (0.2)	4.2 (0.1)	3.8 (0.1)
22:4	0.8 (0.1)	0.9 (0.1)	0.7 (0.2)	0.8 (0.1)	0.6 (0.1)**	0.7 (0.1)
22:6	4.4 (0.4)	4.4 (0.1)	4.0 (1.2)	3.7 (0.1)	3.9 (0.1)	3.4 (0.3)
Phosphatidylethanolamine						
16:0	10.1 (0.1)	9.8 (0.2)	9.8 (0.2)	9.5 (0.4)	9.3 (0.2)	9.2 (0.3)
18:0	21.2 (2.6)	23.3 (0.3)	23.1 (0.2)	20.0 (0.5)	19.5 (0.8)	20.4 (0.5)
18:1	21.8 (0.9)	23.8 (0.5)*	20.0 (2.8)	33.2 (0.9)	33.0 (0.6)	32.5 (0.8)
20:4	12.6 (0.5)	11.5 (0.1)***	11.6 (0.2)	8.4 (0.2)	8.7 (0.4)	8.4 (0.1)
22:4	5.2 (0.1)	4.9 (0.1)*	5.0 (0.1)	4.7 (0.1)	4.8 (0.2)	5.0 (0.1)
22:6	21.1 (0.2)	21.6 (0.5)	21.4 (0.4)	15.0 (0.6)	16.0 (1.0)	16.2 (0.9)
Phosphatidylserine and phosphatidylinositol						
16:0	2.7 (0.2)	2.4 (0.2)	3.2 (0.7)	2.4 (0.1)	2.9 (0.3)	2.7 (0.1)
18:0	38.8 (6.3)	36.0 (1.4)	33.8 (2.0)	35.0 (0.5)	37.2 (3.5)	35.1 (1.0)
18:1	13.3 (1.2)	14.5 (0.4)	16.5 (0.8)***	21.3 (0.3)	23.4 (1.4)	23.7 (0.2)
20:4	12.5 (1.7)	12.4 (0.8)	12.3 (0.6)	14.0 (0.3)	12.1 (1.0)	12.5 (0.7)
22:4	2.7 (0.4)	2.9 (0.1)	3.1 (0.2)	3.3 (0.1)	2.8 (0.2)***	3.2 (0.1)
22:6	26.5 (3.4)	28.2 (1.3)	28.3 (0.4)	18.2 (0.1)	16.4 (0.6)***	18.4 (0.5)

*$P=0.07$ v. control; **$P<0.05$ v. control; ***$P<0.01$ v. control (Dunnet's test).

1. The figures given are mean percentages (s.e.m.) of the total fatty acid in each phospholipid class.

alcoholics but incomplete in the brains of chronic alcoholic patients.

The failure to detect an increase in T_1 in the brain of intoxicated chronic alcoholic patients or in rats intoxicated long-term may be because alcohol has a lower T_1 than water. In none of the studies measuring water content directly (Besson *et al*, 1989*d*) does water content alter in tissue with long-term exposure to alcohol and those in which correlations between T_1, T_2 and water content are made suggest that T_2 is more closely related to water content and T_1 is less so. Hydration effects therefore do not seem to be relevant to T_1 change in chronic non-intoxicated alcoholics, although this remains a possible explanation of the T_1 depression or normalisation in chronic alcoholic subjects when intoxicated and when non-dependent subjects are administered alcohol (Mander *et al*, 1985, 1989).

Relaxation times are related to water content and the 'free-to-bound' state of water in the tissue (Mathur de Vre, 1984). Bell *et al* (1987) have shown that in brain tumours T_1 measured on images correlates with water content measured directly. In rat brain T_1 measured *in vitro* using MR spectrometry correlates with water content measured directly (Besson *et al*, 1989*d*).

The lack of correlation between T_1 and water content in chronic alcoholics suggests that the mechanism of T_1 change is a complex one. The polymer gel model allows the relationship between water content, structure and relaxation times to be studied. Water content can be varied and its structuring altered by using gels of differing pore size and differing biochemical structure of gel framework. Using this model Murase & Watanabe (1989) have demonstrated that relaxation times can vary with altered structuring of water despite a constant water content. The cell membrane, composed largely of phospholipids and lipids, may act as a frame influencing water structure.

Table II shows the membrane phospholipid composition of brain of control rats and rats chronically fed 10% (w./v.) ethanol in calf-milk replacement (Corbett & Leonard, 1984) together with a normal solid diet, then sacrificed during the withdrawal (six rats) and post-withdrawal (six rats) phases by decapitation without anaesthesia. The brains are dissected and stored at −80°C and phospholipid analysis carried out using gas–liquid chromatography. In the cortex and mid-brain there is a reduction in polyunsaturated fatty acids during the withdrawal phase in the phosphatidylethanolamine layer of the cortex samples and the phosphatidylinositol and phosphatidylserine layers of the mid-brain samples. Changes in the structuring of the membrane phospholipids is likely to influence the structuring of intracellular water and therefore its relaxation time. This presents a parsimonious explanation of the T_1 changes. The fact that the T_1 changes do not entirely recover with abstinence in long-term chronic alcoholic patients suggests that these membrane changes are not completely reversible.

Conclusion

Magnetic resonance imaging presents a considerable advance in imaging structural change in neuropsychiatric disease states. These involve the detection of lesions and of brain atrophy – both generalised and focal. Changes in dimension of brain areas can also be measured. The measurement of brain-tissue relaxation times may also help in the characterisation of tissue pathology, the structural and biochemical significance of which is currently being investigated.

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Psychiatry and the New Magnetic Resonance Era

T. LOCK, M. T. ABOU-SALEH and R. H. T. EDWARDS

A non-invasive magnetic resonance 'brain biopsy'?

Psychiatry's lack of understanding of the pathogenesis of mental disorders has resulted in the attempt, within the antipsychiatry movement, to persuade the world that mental disorder does not exist (Szasz, 1961). Progress towards understanding the underlying biological bases of psychiatric syndromes has been impeded by two factors: (a) a most effective physical barrier – the skull; and (b) dichotomous thinking of structure on the one hand and function on the other.

Up to the advent of neuroimaging techniques, research access to the intricate structure and complex function of the living human brain was via accidental or iatrogenic trauma, or indirect via a vast battery of chemical and biochemical techniques. X-ray computerised tomography (CT) and magnetic resonance imaging (MRI) can now display soft-tissue structural abnormalities *in vivo*; this has contributed to the recent upsurge in interest in organic changes associated with major functional disorders (*Lancet*, 1989). MRI is superior to CT as a psychiatric diagnostic tool in many respects, one being that it offers evidence of organic pathology when structural alterations are not obvious (Drayer, 1988). The dilemma of 20th-century psychiatry is that functional disorders are diagnosable, by contemporary operational criteria, only in the absence of organic pathology. We must, therefore, conclude that even the 'superior magic' of MRI has its limitations as far as functional psychiatry is concerned.

The powerful technique of magnetic resonance spectroscopy (MRS) has been used by biochemists and physicists for over 40 years to obtain chemical information from *in vitro* samples. Over the last 10 years, clinical medicine has seen the development of whole-body superconducting MR scanners capable of human *in-vivo* MRS and MR spectroscopic imaging (MRSI).

Magnetic resonance spectroscopy is unique. Its nearest rival is the invasive tissue biopsy. It is the only technique in clinical medicine that provides non-invasive access to living chemistry *in situ*. When combined with MRI, an integrated flexible MRI/MRS examination (Griffiths & Edwards, 1988) unites anatomical structure, pathological function and biochemistry. MRS therefore provides a link between the biochemical understanding of disease and the pathophysiology of medicine (Radda *et al*, 1989). The strengths of MR are: that it is completely non-invasive; that it does not expose patients to ionising radiation; that it has no known side-effects; and that it is suitable for longitudinal studies. The weakness of *in-vivo* MRS is its insensitivity (Chance, 1989).

The "window on metabolism" (Bottomley *et al*, 1989) offered by MRS allows access to ^{1}H, ^{13}C, and ^{31}P metabolites in well documented bioenergetic pathways – membrane metabolites, metabolites of aerobic and anaerobic respiration and the citric acid cycle, some amino acids and neurotransmitters and intracellular pH. Intra- and extracellular sodium and the pharmacokinetics of lithium and fluorinated pharmaceuticals can also be measured. The major thrust to date of clinical MRS has been in high-energy phosphate metabolism, where over 1000 patients have been examined (Radda *et al*, 1989). The reader is referred to the following reviews: Drayer (1988), Bottomley (1989), Radda *et al* (1989), Griffiths & Edwards (1988) and Radda (1986).

The first brain studies were published in 1983/84 (Cady *et al*, 1983; Bottomley *et al*, 1984; Hope *et al*, 1984), and the technical feasibility of MRS as a research probe has already been established (Bottomley, 1988; Radda *et al*, 1989). It has the ability to tackle problems in a fundamental way and provide new information about the biochemical basis of disease. Phosphorus MRS has a clinical role in the investigation of inborn errors of muscle metabolism and has prognostic value in birth-asphyxiated infants and other ischaemic states.

Clinicians using MRS face four major challenges (Bottomley, 1988; Radda *et al*, 1989): (a) obtaining good-quality spectra from a defined volume of tissue in a time acceptable to patients; (b) interpreting and understanding new chemical information from patients in the context of modern biochemistry; (c) quantifying differences between normal and disease states; and (d) applying MRS information to disease diagnosis and to patient management. A fifth, of particular relevance to psychiatry where polymorphism is encountered within any diagnostic category, should be added: careful selection of 'paradigm patients' (Griffiths & Edwards, 1988).

Little has gone before MRS with which results can be compared. Clinical studies often neglect technical and biological difficulties, resulting in careless interpretations and dubious conclusions (Frahm *et al*, 1989).

The pressure is now on clinical scientists to develop clinical applications of the tool for the benefit of their respective subspecialties. The MRS challenges have been met by other neuroscientists, but by very few psychiatrists. Why have we been so slow to exploit the tool? One reason may be lack of access to the necessary hardware and/or non-availability of clinicians trained in its use. Another reason may be the failure of the psychiatric diagnostic process in general.

Principles of clinical magnetic resonance spectroscopy

The principles of MR are complex and the reader is referred to existing texts (Shaw, 1988). MRI is the subject of the paper by Besson in this supplement, so here we concentrate on MRS techniques.

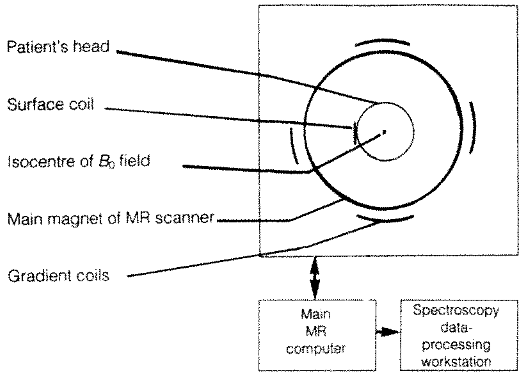
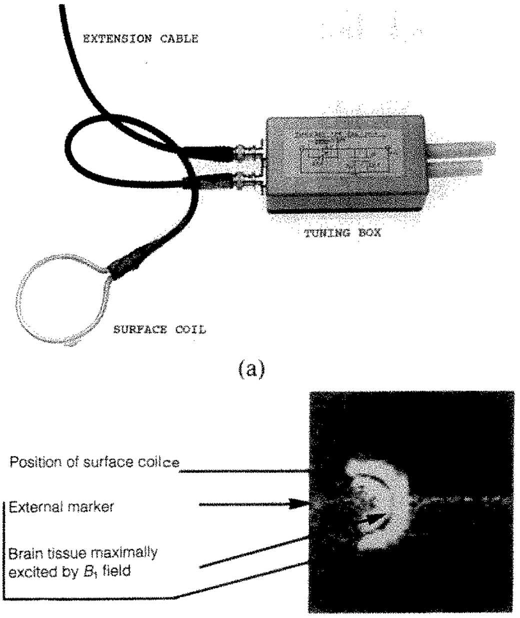


FIG. 1 Schematic diagram of the MRS hardware components – cross-section through magnet isocentre.



(a)

(b)

FIG. 2 (a) A transmit/receive surface coil, diameter 6.5 cm. The surface coil is a single turn of copper wire. It has been tuned to the Larmour frequency of phosphorus. The tuning and matching box is also shown. (b) A coronal ^{1}H image of brain tissue obtained using the coil shown in (a). The maximum sensitivity of a surface coil is limited to a hemisphere beneath the coil. The radius of this hemisphere equals the radius of the coil.

The necessary hardware is represented in Fig. 1. The static (B_0) field of the scanner is in the direction of the magnet tunnel (z) axis and is produced by a high-field (1.5–2.5T) superconducting magnet. Homogeneity of the B_0 field is critical for spectroscopic studies. Magnet inhomogeneities are minimised by 'shimming' the magnet.

A radiotransmitter (the surface coil) transmits a radiofrequency (RF) pulse which creates the RF or B_0 field at right angles to the z axis (Fig. 2). The radiofrequency (Larmour frequency) is determined by a constant, unique to a selected nucleus, and is related to the strength of the B_0 field. The raw MR signal is received by the same or a different surface coil. Gradient coils superimpose their fields on the B_0 field in orthogonal planes for spatial encoding of the MR signal. The main MR computer drives the RF and gradient fields and computes the raw MR signal, which is then processed into spectra on a spectroscopy data-processing workstation.

Only atomic muclei possessing the property of paramagnetism when in the B_0 field are suitable candidates for MRS (Table I). Furthermore, for the production of an MR signal of detectable intensity, (a) the magnetism of these nuclei must be sufficiently sensitive to the B_1 field, (b) the nuclei must be in sufficient concentration in the tissues, and (c) only metabolites/ions which are in solution are 'MR-visible'. The 'overall sensitivity' of the selected nuclei is the sensitivity of the nucleus to MR multiplied by its local concentration in tissue. The current detection limit of such nuclei is about 10^{-6} that of water protons in any given volume of interest (VOI) (Bottomley, 1989). The only way of improving the detectability of relatively insensitive nuclei is to increase the size of the volume from which signal is

TABLE I

Characteristics of atoms suitable for MRS/MRSI and detectable metabolites in brain in-vivo *at 1.5T field strength*

Element	*Isotope*	*Atomic number*	*Mass number*[1]	*Suitability for type of MR technique*[2]	*MRS-detectable metabolites*[3]	*Overall sensitivity*[4]
Hydrogen	^{1}H	1	1	MRS	Water Lactate Nicotinic acid amide Glutamate Glutamine Aspartate Taurine Gamma-aminobutyric acid Alanine Creatine Choline	1
Lithium	^{7}Li	3	7	MRS MRSI	Ion – no metabolites	
Carbon	^{13}C	6	13	MRS, POCE MRS	Ethanol Fat Glycogen Glutamate Lactate Choline Glycerol	
Oxygen	^{16}O	8	16	–		
Fluorine	^{19}F	9	19	MRS, MRSI	Fluorinated pharmaceuticals	$\sim 7\times10^{-5}$
Sodium	^{23}Na	11	23	MRSI	Ion – on metabolites (intracellular and extracellular ions can be distinguished)	
Magnesium	^{24}Mg	12	12	–		
Phosphorus[5]	^{31}P	15	31	MRS	PME Pi PDE PCr γATP αATP βATP	$\sim 4.5\times10^{-5}$

1. Mass number = sum of protons and neutrons in atomic nucleus.
2. Suitable nuclei for MR spectroscopic techniques must contain an unequal number of protons and neutrons.
3. For additional details see Bottomley (1988).
4. Overall sensitivity relative to ^{1}H(proton) imaging = sensitivity, per nucleus (%) × concentration of metabolite in tissues (Perman & Turski, 1989).
5. PME = phosphomonoester, Pi = inorganic phosphate, PDE = phosphodiester, PCr = phosphocreatine, ATP = adenosine triphosphate (γ, α and β positions of ^{31}P nucleus).

detected and/or average a number of signals together to improve the ratio between signal to background noise (SNR). The rate at which the RF pulse is repeated is known as the repetition time (TR). Clinical MRS studies are usually run using a fast TR. When the TR is shorter than the T_1 (spin lattice) relaxation time of any given metabolite, saturation effects are observed. Saturation effects result in a reduction in signal.

Different metabolites containing a selected MR-sensitive nucleus resonate at slightly different frequencies because of the minute magnetic effects of the other atoms in a given metabolite. This MR phenomenon – chemical shift – is described in units of parts per million (p.p.m.) relative to the central radiofrequency (Figs 3, 4). The peaks of a spectrum represent metabolites containing a selected MR-sensitive nucleus; the baseline represents background

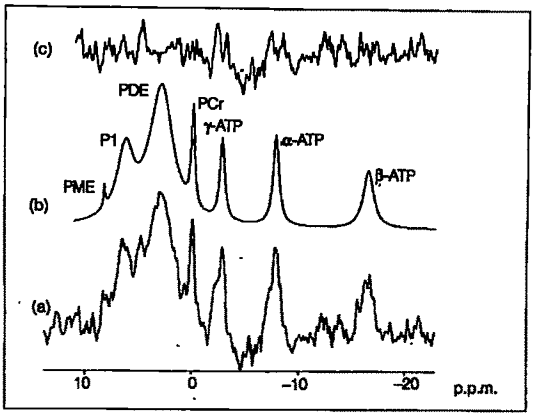


FIG. 3 An *in-vivo* ^{31}P spectrum from an ID-CSI (chemical shift imaging) 'disc' of brain tissue: (a) original processed spectrum, (b) the spectrum after a computerised curve-fitting routine, and (c) original spectrum with the fitted spectrum subtracted. This spectrum represents *in-vivo* phosphorus metabolism in cortical grey and white matter (see Fig. 6 (d)). The broad hump underlying the PME, Pi, PDE and PCr resonances is derived from tissue phospholipids and mineral phosphates in bone. These phosphorus metabolites are not in solution and are therefore unable to resonate freely.

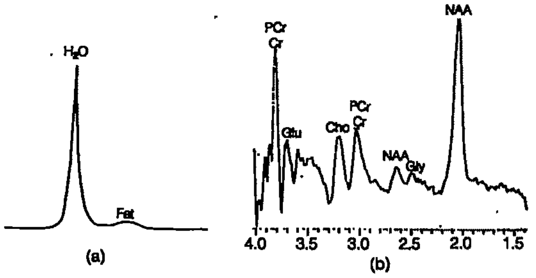


FIG. 4 The ^1H spectrum of brain tissue. (a) Without solvent suppression, the only ^1H metabolites detectable in the spectrum are water and fat. (b) With solvent suppression, several metabolites are seen. Other metabolites are better visualised by changing the acquisition parameters. Lactic acid resonates at position X but is not visible in this spectrum of a healthy resting volunteer. Note that the scale of these two spectra differ. Were they drawn to the same scale, the H_2O peak in (a) would be several feet high.

noise. Relative metabolite concentrations are obtained by calculating the area under each peak.

It is possible, with MRSI, to construct metabolic maps (or images), but it will be deduced that *in-vivo* biochemistry will never be imaged with the same spatial resolution that characterises ^1H MRI and that there is a marked discrepancy between the time taken to obtain proton images and MRS biochemical information. The concepts of acquisition time and quality of signal (Fig. 5) are major considerations in any MRS examination; this is discussed in greater detail after the next section.

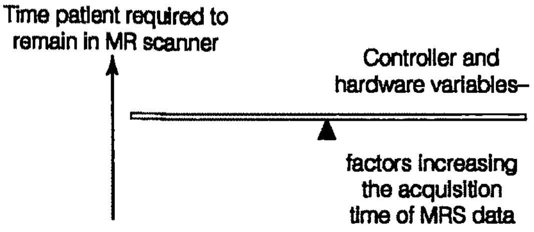

Time patient required to remain in MR scanner
Controller and hardware variables–
factors increasing the acquisition time of MRS data

FIG. 5 The art of clinical and technical compromise: balancing the quality of *in-vivo* MRS data to the time required to acquire it. Controller variables include: TR too slow, making acquisition time too long; TR too fast, giving saturation effects; NAV (number of free induction decays (FDIs) averaged) too few, giving poor SNR; selected volume too small, giving poor SNR; gradient fields (for phase encoding) produce eddy currents, giving a reduced SNR; and spatial localisation technique may increase acquisition time. Hardware variables increasing duration of scan include: choice of RF coils incorrect for volume of interest; RF coil badly positioned/badly tuned; suboptimum B_0 field homogeneity.

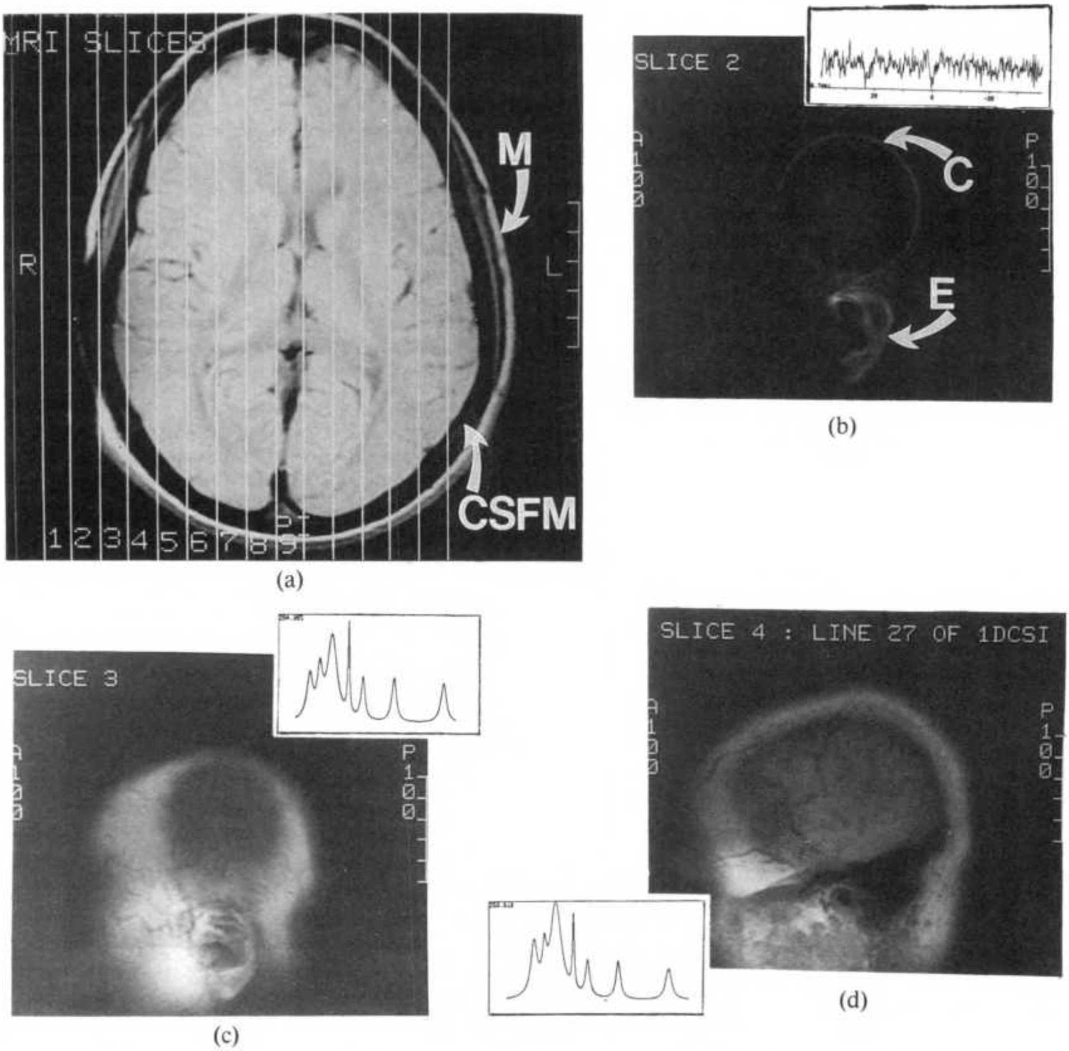
Clinical applications of MRS

The following accepted chemical abbreviations are used throughout this section. They are displayed here for ready reference.

ADP	adenosine diphosphate
ATP	adenosine triphosphate (γ, α, and β positions of ^{31}P nucleus)
GPC	glycerophosphorylcholine
GPE	glycerophosphorylethanolamine
NAA	n-acetyl aspartate
PCh	phosphorylcholine
PCr	phosphocreatine
PDE	phosphodiester
PEt	phosphorylethanolamine
Pi	inorganic phosphate
PME	phosphomonoester
POCE	proton observe carbon edit
^1H	hydrogen (protons)
^7Li	lithium
^{13}C	carbon
^{19}F	fluorine
^{23}Na	sodium
^{31}P	phosphorus

Phosphorus MRS

The most widely used MRS technique has been that with ^{31}P. The phosphorus spectrum (Fig. 3) obtained from the brain of a normal volunteer reveals seven peaks representing the resonances of PME, Pi, PDE, PCr, γ-ATP, α-ATP, and β-ATP.



(a)

(b)

(c)

(d)

FIG. 6 The integrated MR examination: radiodiagnostic MR images and *in-vivo* phosphorus biochemistry. (a) ^{1}H axial proton density image showing planes of ID-CSI slices (1–9). (b) ^{1}H sagittal T_1-weighted image of slice 2 from (a). Note (with reference to (a)) that the three-dimensional volume represented by this two-dimensional image contains ear (E), surface coil (C), skin and temporalis muscle (M), cerebrospinal fluid and meninges (CSFM). Bone is not visualised by MRI. The phosphorus spectrum is undetectable (inset). (c) ^{1}H sagittal T_1-weighted image of slice 3. The three-dimensional volume contains meninges and CSF and some cortex. The ^{31}P spectrum (inset) reflects phosphate metabolism in all of these tissues/fluids, and the biochemical information obtained has little clinical meaning. (d) ^{1}H sagittal T_1-weighted image of slice 4. The three-dimensional volume contains cortical grey and white matter. The ^{31}P spectrum (inset) is displayed in detail in Fig. 3.

The ^{31}P spectra of phosphorus metabolites in healthy heterogeneous brain tissue reveal no significant interhemispheric differences and concentrations and compare well with biochemical assays of rat brain (Bottomley *et al*, 1984). The broad hump underlying the PME, Pi, PDE and PCr resonances derives from tissue phospholipids and mineral phosphates in bone (Fig. 6).

Phospholipid metabolism

The two peaks for PME and PDE are thought to represent brain phospholipid metabolism. The peaks are larger than those of muscle spectra owing to the high lipid content of white (16%) and grey (6%) matter (Bottomley *et al*, 1984) and show a general increase from superficial (predominantly grey matter) deep structures (Cadoux-Hudson *et al*, 1989). The ajor constituent of the PME resonance is PEt, precursor of phosphatidylcholine (lecithin), a embrane phospholipid. The PDE resonance has een assigned to GPC and GPE. Ninety per cent f the PDE resonance in brain comes from the hospholipid bilayer of myelin sheaths and the emainder from membrane degradation products. he clinical potential of the PME and PDE resonances that they are markers for disturbed membrane etabolism in disease states. Other phospholipid etabolites (e.g. choline and fat) are accessible to H (Fig. 4) and ^{13}C MRS.

rain bioenergetics

he brain has limited energy stores and under normal hysiological conditions the energy demands of he brain are met almost exclusively by glucose McCulloch, 1982; Radda *et al*, 1989). The chemical eactions involved in the supply and utilisation of nergy (Fig. 7) are centred on ATP – by far the major emand for which comes from the neurophysiological rocesses of ion pumping and neuronal firing. The oncentration of ATP is strictly controlled and is inked via regulatory processes to the demand for TP (rate of ATP hydrolysis) and to mitochondrial xidative phosphorylation of glucose (rate of aerobic TP production via the Krebs' cycle). A shift to non-xidative (anaerobic) metabolism in the cytosol occurs when aerobic ATP production is inadequate (e.g. in ischaemic and anoxic states) and results in an accumulation of lactic acid and a corresponding reduction in intracellular pH (Radda, 1986).

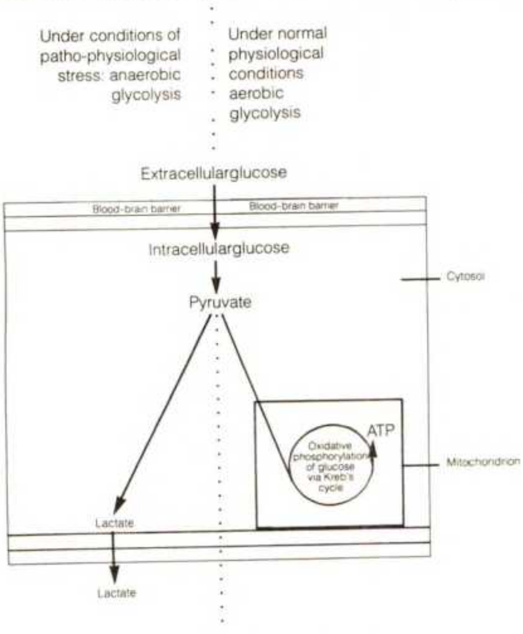

Under conditions of patho-physiological stress: anaerobic glycolysis
Under normal physiological conditions aerobic glycolysis
Extracellularglucose
Blood-brain barrier
Blood-brain barrier
Intracellularglucose
Cytosol
Pyruvate
ATP
Oxidative phosphorylation of glucose via Kreb's cycle
Mitochondrion
Lactate
Lactate

FIG. 7 Schematic diagram of brain bioenergetics.

The five other resonances of the ^{31}P spectrum (Pi, PCr, γ-ATP, α-ATP and β-ATP) give direct access to these reactions and their regulation (Radda, 1986, 1990; Radda *et al*, 1989). Regulation may be considered at several levels, one of which (of relevance to psychiatry) is neurotransmitter activation of second messenger systems which modulate the activity of individual enzymes or coupled processes.

The high-energy phosphates are ATP, ADP, and PCr. The γ-ATP and α-ATP resonances of the ^{31}P spectrum contain signal from other phosphate metabolites so the β-ATP peak is the most reliable indicator of tissue ATP levels. The phosphate moiety, Pi, is released when ATP is cleaved to form ADP. The position of its resonant frequency, relative to a reference point in the ^{31}P spectrum, may be referred to a pH titration curve to provide an accurate non-invasive measurement of tissue pH.

Lactic acid is directly accessible by ^{1}H MRS. PCr acts as an energy 'shuttle' (Radda, 1986; Griffiths & Edwards, 1988) between sites of ATP production and ATP utilisation. The reaction PCr + ADP = ATP + creatine serves to prevent short-term ATP deficits without consuming oxygen. The rapid depletion of muscle PCr and ATP and corresponding acidosis that occurs within seconds of vigorous exercise or ischaemia (Edwards *et al*, 1982) is one of the most spectacular demonstrations of living biochemistry by MRS. Similar findings have been shown in an animal model of status epilepticus (Petroff *et al*, 1984).

Because ^{31}P MRS has the ability to follow metabolic reaction rates in response to stress of some sort, ^{31}P MRS has been used to investigate clinical conditions associated with abnormalities in energy supply. Clinical studies fall into three categories (Bottomley *et al*, 1989; Radda *et al*, 1989; Griffiths & Edwards, 1988): (a) studies of disordered intracellular signalling due to inborn errors of metabolism, (b) studies of abnormal glucose or oxygen supply (ischaemia, infarction, trauma and necrosis), and (c) tumour metabolism and response to treatment (see Table II for an overview of ^{31}P MRS studies of the brain).

Studies of psychiatric patients

The few preliminary MRS studies of psychiatric patients have been summarised in Table III. Avenues for future investigations include the assessment of brain bioenergetic responses to psychoactive drugs or physical therapies known to induce alterations in

TABLE II
^{31}P MRS studies of the human brain

Condition	*Abnormality noted*	*Interpretation*	*Reference*
Infants			
Normal	↑ PME	↑ Membrane synthesis	Cady *et al* (1983) Hope *et al* (1984)
Birth asphyxia	Acidosis rare No change in first 16 hours. Thereafter ↓ PCr:Pi up to 100% ↓ PCr:ATP up to 25%	PCr:Pi$<$0.8 associated with poor prognosis and neurodevelopmental outcome	Hamilton *et al* (1985)
	After 13 days – slow return to normal		Azzopardi *et al* (1989*a*,*b*)
Normal (absolute quantification of ^{31}P metabolites)	↑ in ^{31}P metabolites with gestational age ↑ PME	↑ metabolites not due to ↑ cellularity of brain	Cady & Azzopardi (1989)
Birth asphyxia (absolute quantification)	Concentrations below 2 s.d. of normal mean PCr:Pi below confidence limits	Significant deviation of concentrations associated with fatal outcome/multiple impairments (two fatal cases had normal concentrations)	
Minimally affected birth – asphyxiated infants	Regional heterogeneity of PCr:Pi ratios	Deeper tissues more vulnerable to asphyxia	Radda *et al* (1989)
Adults: ischaemia[1]			
Acute cardiovascular accident (CVA)	↓ PH first day* ↓ PCr/Pi first week	Abnormalities noted in acute stage	Levine *et al* (1987) Welch *et al* (1985)
Chronic CVA with residual neurological defect	All ^{31}P metabolites reduced up to 40%. Ratios normal. ↑ pH or normal	Death of cells Surviving cells function normally	Bottomley *et al* (1986)
		^{31}P ratios a sensitive marker for infarction for a limited time only	
Transient ischaemic attack – carotid stenosis	Localised normal or PCr:ATP	Surgery normalises ^{31}P ratios in some patients	Radda *et al* (1989)

Adults: neoplastic disorder			
Astrocytomas	↓ absolute concentration PDE, PME and PCr Qualitative changes in PME metabolites ↑ PME, ↑ PDE, ↑ pH PCr:Pi	Means of differentiating astrocytomas from meningeal extracerebral tumours	Hubesch *et al* (1990)
Variety of brain tumours		↑ Membrane synthesis in rapidly mitosing cells	Segebarth *et al* (1987)
Adults: metabolic disorder			
Mitochondral myopathies[2] (3 paradigm studies)	↑ Pi:PCr and ↑ Pi:ATP after exercise ↓ pH after exercise	Changes in brain bioenergetics secondary to systemic effects	Radda *et al* (1989)
Mitochondral encephalopathies[3] (4 rare syndromes)	↓ PCr:Pi, ↓PCr:ATP, ↓PDE:ATP in brain *not* after exercise	Primary reduced availability of energy substrate due to abnormal brain mitochrondral phosphorylation of glucose	Eleff *et al* (1989)
Adults: trauma			
13 patients; acute head injury; 15–30 days after trauma	↓ PCr:Pi in traumatised hemisphere ↓↓ or no ATP		Lenkinski *et al* (1989)
Adults: neurological disorder			
18 patients: multiple sclerosis different stages[1]	↓ PDE	Relationship to rate of progression of illness	Mooyart *et al* (1989)
Refractory complex partial seizures (TLE)[1] (absolute quantification)	↑ pH and ↑ Pi in localised seizure foci	↑ pH pathological mechanism for seizures or result of seizures?	Hubesch *et al* (1989*a*,*b*) Weiner *et al* (1989)

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[1] See also ^{1}H MRS studies of the brain.

[2] Mitochondral myopathy = inborn error of metabolism affecting mitochondral phosphorylation reactions in *muscle*.

[3] Mitochondral encephalopathy = inborn error of metabolism affecting mitochondral phosphorylation reactions in *brain*.

TABLE III
MRS studies of psychiatric patients

MRS technique	Condition	Abnormality noted	Interpretation	Reference
^{31}P *in-vitro* studies of acid extracts of post-mortem brain	Senile dementia of the Alzheimer type (SDAT) Huntington's chorea	Large ↑ PME, Small ↑ PDE, both correlate to number of plaques	Fault in membrane synthesis. PME could interact with NMDA–glutamate receptors to act as false neurotransmitter. Membrane aberrations may be early metabolic events in pathogenesis of AD	Barany *et al* (1985) Pettegrew *et al* (1987, 1988*a*,*b*)
^{31}P *in-vivo* MRS, in deep white matter	4 Huntington's, 1 Alzheimer's, 2 Parkinson's patients	No change in ratios	*In-vitro* findings not reproducible *in-vivo*	Smith *et al* (1986)
^{31}P *in-vivo* MRS, in deep white matter	2 patients with Binswanger's dementia	Small ↑ PDE		Smith *et al* (1986)
^{31}P *in-vivo* MRS	Healthy elderly and SDAT with deep white matter lesions on MRI	↓ PDE ↓ PME ↓ ATP	Non-specific changes	Sappey–Marinier *et al* (1989)
MRI and ^{31}P *in-vivo* MRS, 3 cm-thick axial section; degree atrophy determined from MRI	Mild to moderate AIDS dementia, 8 patients	All metabolite concentrations reduced but ratios normal. No significant ischaemic or metabolic derangement; reduced concentration not due to brain atrophy	Loss of ^{31}P signal due to loss of metabolically active cells, probably neurons	Bottomley *et al* (1989)
^{31}P and ^{1}H MRS (absolute quantification)	AIDS dementia	↓ ATP:Pi in selected regions; no correlation with necrosis or deep white-matter lesions	Loss of ^{31}P signal due to loss of metabolically active cells, probably neurons	Weiner *et al* (1989)
^{31}P *in-vivo* MRS, spectra localised to dorsal pre-frontal cortex	'First-break' psychoses: schizophrenia (3 patients), schizophreniform (1), atypical psychoses (4), unmedicated at entry	↓ PME ↑ PDE and ↓ α-ATP at entry, more pronounced after 4 weeks of neuroleptics.	↑ breakdown of membrane phospholipids; knock-on effect on membrane protein receptors, channels and second messenger signalling. ↓ utilisation of PCr–hypofrontality?	Keshavan *et al* (1989)
^{31}P *in-vivo* MRS, minimally localised volume of left temporal lobe containing heterogeneous brain tissue	Schizophrenics on neuroleptics (12 patients)	No significant differences in metabolite ratios or concentrations, ↑ pH	pH change may be statistical error or due to neuroleptic treatment	O'Callaghan *et al* (1989)
^{31}P MRSI and MRI	18 demented patients Non-Alzheimer's excluded by CT and ^{1}H MRI scans	Hypointensities and hyperirregularities	Is patchy hypointensity due to patchy hypometabolism secondary to blood flow or glucose metabolism? Findings compatible with PET and SPECT findings	Noguchi *et al* (1989)
^{19}F MRS, minimally localised volume containing heterogeneous brain tissue	1 schizophrenic on trifluoroperazine (120 mg daily)	See text	See text	Komoroski *et al* (1989)
^{1}H MRS, 16–24 cm^{3} volume of deep structures within left hemisphere	5 adults with phenylketonuria on dietary treatment	↑ levels of phenylalanine of controls	First MRS observation phenylalanine in human brain	Novotny *et al* (1989)

energy demands. Although ^{31}P MRSI has been used as an alternative to 2-deoxyglucose metabolic mapping techniques (Ackerman *et al*, 1980; Noguchi & Toshirou, 1989), the spatial resolution of these images is greatly inferior to images from positron emission tomography (PET) and the practical use of ^{31}P MRSI is debatable (Lear, 1990).

Hydrogen and carbon MRS

Lactic acid (the end-product of anaerobic metabolism), glycogen, the citric-acid cycle and its metabolites, some amino acids and neurotransmitters, and membrane lipids are present in brain in high natural abundance and are accessible to ^{1}H and ^{13}C MRS. The techniques have only recently been employed for clinical studies so these metabolites present a major untapped clinical resource. The major hurdle in ^{1}H MRS is the suppression of the strong water and fat resonances which swamp the smaller resonances of other ^{1}H-containing metabolites (Fig. 4). Special water-suppression RF pulse sequences have been designed to achieve this.

Hydrogen is about 15 times more sensitive than other paramagnetic nuclei, so ^{1}H MRS studies can usually be completed within a relatively short time and with relatively good spatial resolution. A few preliminary studies have been published (Table IV).

Only 1% of carbon in the body is paramagnetic ^{13}C. The potential of ^{13}C MRS is in proton-observe carbon-edit (POCE) MRS (Shulman *et al*, 1990). In POCE MRS, a non-radioactive ^{13}C label is attached to glucose, which is then administered. The rate of the incorporation of the ^{13}C label into ^{1}H metabolites (e.g. glycogen and lactate) is monitored by ^{1}H MRS. The technique has only recently been used in humans. A POCE study of electroconvulsive shock in rats has shown a prolonged increase in cerebral lactate level while cerebral energy stores and intracellular pH (measured by ^{31}P MRS) remained normal (Petroff *et al*, 1989).

Sodium and lithium MRS

Sodium is found in natural abundance in the brain, whereas lithium is detectable only in people on lithium treatment. Both are ions and are found in the body in only this chemical form. The MR signals from ^{23}Na and ^{7}Li have been processed into images depicting the heterogeneous concentration patterns of the respective ion (Renshaw *et al*, 1985; Perman & Turski, 1988) but the spatial resolution of these images is low.

The extracellular pool of sodium is accessible to membrane permeability agents which change its chemical shift, so ^{23}Na spectroscopy has the potential of differentiating the intra- and extracellular pools of sodium. Obvious applications are disorders involving the sodium–potassium pump and/or disorders affecting the blood–brain barrier, but clinical studies have not been undertaken. Sodium imaging has demonstrated elevations in sodium signal intensity in strokes, haemorrhages, brain tumours and seizures (Perman & Turski, 1988; Drayer, 1988).

There is an obvious psychiatric use for ^{7}Li MRS. The technique has been used to follow the uptake and distribution kinetics of lithium administered to two psychiatrically normal volunteers (Renshaw & Wicklund, 1988). Eight hours after the ingestion of a single 1200 mg dose of lithium carbonate, tissue levels lagged serum levels, and lithium concentration was greater in muscle than in brain. After seven days of 600 mg b.i.d. slow-release lithium, brain lithium levels remained lower than those of muscle, in turn lower than those of serum. These findings are compatible with conventional studies of lithium levels in serum and cerebrospinal fluid (CSF), as were the MRS-defined elimination kinetics: the half-time to clear lithium from muscle was 24 hours, 30 hours for serum and 48 hours for brain. Renshaw & Wicklund acknowledged that they had not addressed the likely regional heterogeneity of brain lithium concentrations, but another group (Ramprasad *et al*, 1990) are developing a technique whereby quantitative lithium images can be superimposed on proton images so that regional differences in brain lithium concentration can be seen with precise anatomical localisation.

Fluorine MRS

Fluorine has such a low natural abundance in the brain that it is normally undetectable, but ^{19}F MRS has been used to follow the pharmacokinetics of fluorinated drugs in animal studies (Wirwicz *et al*, 1983; Bartels *et al*, 1986; Arndt *et al*, 1988). The first observation of the antipsychotic trifluoperazine in the brain of a male schizophrenic was reported recently (Komoroski *et al*, 1989). The patient was on a dose of 120 mg/day. The brain concentration of the drug within a heterogeneous tissue volume was comparable with concentrations in rat brain. By calculation, a typical 1500 ml brain would contain 24–39 mg of drug and its metabolites: thus ^{19}F MRS provided clear evidence that the drug accumulated in brain. Furthermore, a small shift in the resonant frequency was noted and this was attributed to the binding of the drug to its receptor sites.

TABLE IV

Other MRS studies of the human brain

MRS technique	*Condition*	*Abnormality noted*	*Interpretation*	*Reference*
^{1}H and ^{31}P MRS: 80 cm^3 volume (^{1}H), 200 cm^3 volume (^{31}P), of central subcortical structures	Chronic hepatic encephalopathy (3 patients)	↑ glutamine ↓ choline ↑ phosphocholines	Alteration of brain membrane structure	Luyten *et al* (1989*a*,*b*)
^{1}H MRS, 22.5 cm^3 volume, 1 cerebral hemisphere, containing putamen and caudate	Inborn errors metabolism (4 patients), MRI changes in basal ganglia	Differential ^{1}H MRS findings between diagnoses and normals		Jenson *et al* (1989)
^{1}H MRS, volume containing epileptic focus	Focal epilepsy secondary to chronic encephalitis (1 patient)	↑ lactate in seizure focus	Lactic acidosis may contribute to death of excitable cells	Matthews & Arnold (1989)
^{1}H MRS, localised volume containing plaques	Multiple sclerosis (13 patients)	Changes in metabolites in some volumes	Demyelination is a dynamic process; MRS changes may be transient	Narayana *et al* (1989)
^{1}H MRS, localised volume containing posterior corpus callosum	Multiple sclerosis (7 patients), different stages	↓ NAA ↑ Cho:NAA and ↑ Cr:NAA in severely affected patients, ratios normal in milder cases		Arnold *et al* (1989)
^{1}H and ^{31}P MRS, volume containing area infarction	Cerebrovascular accident, subacute to chronic	↑ lactate	Lactate a marker of anaerobic glycolysis when ^{31}P ratios back to normal ↑ lactate a sensitive indicator of completed infarction	Van-Rijen *et al* (1989)
^{1}H MRS, 1.5–6 cm^3 volume	Cerebrovascular accident, ischaemic tissue (penumbra) *around* area of infarct	↑ Ch: NAA	This ratio a sensitive marker of brain injury	Luyten *et al* (1989*a*,*b*)
^{7}Li MRS, minimally localised volume containing heterogeneous brain tissue	See text	See text	See text	Renshaw & Wicklund (1988)
^{7}Li MRSI and ^{1}H MRI	See text	See text	See text	Komoroski *et al* (1990)

In PET studies, radiolabelled fluoro-2-deoxyglucose is the compound used to determine regional cerebral metabolic rate. Non-radioactive ^{19}F MRS therefore opens up new avenues of functional neuroimaging. New fluorine compounds have been synthesised which enhance the ^{19}F signal intensity which may improve the present spatial resolution limits of ^{19}F spectroscopic images.

Factors to consider when evaluating MRS studies

Care should be taken when evaluating MRS results because of the many inter-related patient and technical variables – the man–machine interaction (Griffiths & Edwards, 1988) (Fig. 8). Attention should also be directed to the experimental paradigm.

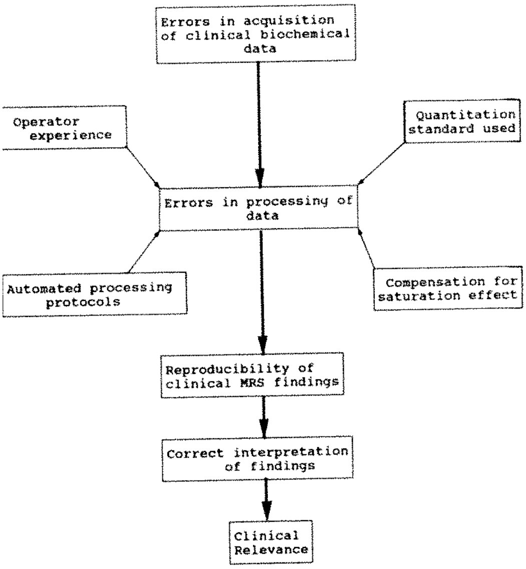
Errors in acquisition of clinical biochemical data
Operator experience
Quantitation standard used
Errors in processing of data
Automated processing protocols
Compensation for saturation effect
Reproducibility of clinical MRS findings
Correct interpretation of findings
Clinical Relevance

FIG. 8 Factors affecting the clinical relevance of MRS findings.

The man–machine interaction

The brain

There are five major considerations in any brain study.

(a) Shape of the human head. The human head is spherical and MR-located volumes of interest are geometric (Ross *et al*, 1989). The architecture of the brain is such that the shapes of brain structures of interest to psychiatrists simply do not conform to orthogonal geometry. Metabolites measured within an MR-defined volume of interest therefore represent the mean concentrations in the whole volume (Fig. 9). This 'partial-volume' effect must be addressed in all MRS studies.

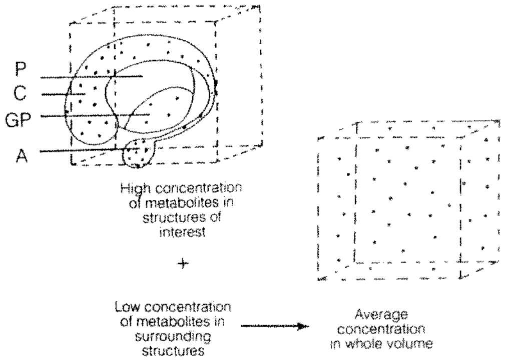
P
C
GP
A
High concentration of metabolites in structures of interest
+
Low concentration of metabolites in surrounding structures
Average concentration in whole volume

FIG. 9 Diagrammatic representation of the effects of 'partial voluming' on spatial resolution of emitted signal. The relative sensitivity and *in-vivo* concentration of metabolites determine the minimal volume of tissue from which signal may be detected. If structures of interest e.g. (C) caudate, (P) putamen, (GP) globus palidus, (A) amygdala contain signal of interest (∴) and surrounding tissues contain none, the spatial location of the signal is lost because of the relatively large volume size.

(b) Regional heterogeneity of structure, function, blood flow and biochemistry within the brain (Chance *et al*, 1987; Hubesch *et al*, 1989). The brain has a rich blood supply and the effect of blood flow itself on metabolite concentration in the brain must be considered. The early ^{31}P MRS studies of brain bioenergetics in birth-asphyxiated infants (Cady *et al*, 1983; Hope *et al*, 1984) did not address the issue of brain heterogeneity. This issue is relevant when regional specificity of pathology is known or suspected. Heterogeneity of PCr:ATP and PCr:Pi ratios has since been demonstrated in minimally affected infants (Radda *et al*, 1989): superficial tissues showed the expected normal phosphate ratios but alterations in metabolite ratios were noted in deeper structures.

(c) Age. A recent study of neonates (Cady & Azzopardi, 1989) showed, by absolute quantification of ^{31}P metabolites, an increase in ^{31}P metabolites with increasing gestational age in normal infants, while birth-asphyxiated infants had reduced concentrations of ^{31}P metabolites in cortex with low or normal ^{31}P metabolite ratios. The effects of ageing on metabolite concentrations in the adult brain are unknown.

(d) Intersubject variation. Human beings have enormous variety and polymorphism. In this context, the range of intersubject variations in biochemistry may obscure fairly large intrasubject variations.

(e) The effects of psychotropic medication. Alterations in brain energy metabolites have been observed in patients commencing neuroleptic medication (Keshaven *et al*, 1989). Accounting for the psychotropic variable is a major consideration in any psychiatric study. The monitoring of sedated patients in the magnet must also be considered.

Psychiatric patients

The prolonged acquisition times of MRS studies demand patience, co-operation and motivation from study subjects – attributes frequently diminished in psychiatric patients. Claustrophobia and excessive patient movement would necessitate the termination of a study. We are aware that one major neuroimaging research group has had great difficulty with the MRI component of their research into Alzheimer's disease for a combination of these reasons. However, it has been shown (Thorp *et al*, 1990) that the acceptability of MRI is at least as high as that of CT scanning, so it is possible that similar difficulties may be avoided with other patient groups.

The art of clinical and technical compromise

It is important to find a reasonable balance between the quality of the MRS signal – defined in terms of the resolution of spectral peaks, the signal-to-noise ratio (SNR) of those peaks, and localisation of the signal-to-brain structures of interest (Frahm *et al*, 1989) – and the time patients are required to lie still. Therein lies the art of clinical and technical compromise (Fig. 5). Any patient examination is planned around a bare minimum of technical requirements in the expectation that the study may have to be terminated prematurely (Young *et al*, 1989).

Sources of technical artefact

Data obtained by different MRS technologies cannot be compared because each method has its own limitations and sources of error (Young *et al*, 1989). Reproducibility errors are introduced by four categories of factors, irrespective of any underlying pathophysiological variation (Fig. 8).

Errors in the acquisition of MRS data

These have been mentioned under the man–machine section. The common, and most important, technical limitation of this interaction is the SNR of individual spectral peaks. Errors in excess of 20% are observed when the SNR is less than 10% (Martin *et al*, 1988). The cost of improving the SNR of the signal from a given volume of tissue is an increase in acquisition time (Fig. 5). It is important to spend time shimming the magnet, positioning the patient and surface coils, and in tuning and matching the surface coils for individual heads before an MRS investigation can commence.

Spatial localisation strategies

Precise spatial location of biochemical information is critical for absolute metabolic quantification (Frahm *et al*, 1989) and for studies of patients with focal pathology. With regard to neurotransmitter studies, where localisation of neuroreceptors is achieved by attaching a detectable label to a pharmaceutical agent which binds to its receptor sites, it is doubtful whether MRS techniques would ever reach the present level of functional localisation achieved by PET – a sensitivity difference of 1000 exists between MRS and PET (Chance, 1989).

Much technical expertise and published work over the last six years has been channelled into improving the spatial localisation of the MR biochemical data.

Numerous localisation strategies have been proposed (Gadian, 1989) but unlike MRI, where there is good consensus on the best localisation technique, no such consensus exists for MRS. Improved spatial localisation may enhance our understanding of the diagnostic information available. On the other hand, spatial localisation techniques may obfuscate diagnostic information by introducing new technical artefacts and/or by prolonging data acquisition time (Ross & Naraimhan, 1989).

The performance of two techniques in use in our MR centre is compared in Table V. Because the sensitivity advantage of larger volumes outweighs the advantages of smaller localised volumes, it is often wise to forgo any more elaborate localisation, particularly if changes are expected to be global, and opt for the largest volume and/or minimal spatial localisation.

The localisation technique currently favoured by some leading MR spectroscopists is image-selected *in-vivo* spectroscopy (ISIS). By the use of this technique, signal from ^{31}P metabolites can be localised to an axial 'slab' of brain tissue, at the level of the ventricles. This 'slab' contains basal ganglia, midline structures, superficial grey and deep white matter.

Quantification methods

Early MRS studies (Edwards *et al*, 1982; Cady *et al*, 1983; Bottomley *et al*, 1984; Hope *et al*, 1984) were qualitative rather than quantitative – that is, they relied upon *relative* quantification of peak areas, where changes in metabolite ratios reflected changes in the steady state of high-energy phosphate metabolites in the brain. Relative quantification is

TABLE V

Spatial localisation: comparison of two ^{31}P MRS techniques

	Pulse and acquire	*ID–CSI*
Description of localised volume	Hemisphere below surface coil defined by B_1 field, related to size of surface coil (Fig. 2 (b))	Gradient fields locate signal from within the sensitive hemisphere of the surface coil to planes parallel with the surface coil. The results of ID–CSI and surface-coil localisation are spatially located 'discs' of cerebral tissue (Fig. 6)
Advantages	Well researched clinical applications Ease of implementation Suitable for large organs, close to the surface Good spectral resolution	
Costs and benefits	Good SNR per unit time	Acquisition time increased by phase-encoding steps; time factors limit NAVs – SNR reduced per unit time
	Heterogeneity of tissues within sensitive volume	Heterogeneity within slice unless slice filled by homogeneous structure
	Coil can be placed anywhere on surface of skull	Phase encoding only in orthogonal planes; axis of RF coil in x or y plane relative to B_0 field
	Suited to dynamic studies of global changes, lasting less than 5 minutes	Not suited to dynamic studies under 5 minutes
		Allows comparison of biochemical content of different 'discs' because signal is collected simultaneously from all discs

reliable (Martin *et al*, 1988) and more straightforward than absolute quantification. The method is adequate for studies in which a patient acts as his/her own control.

Relative quantification has obvious limitations if normal and abnormal groups are to be compared: it is known that ^{31}P ratios may be normal in some conditions (e.g. chronic stroke with obvious neurological deficit and neurodegenerative conditions – see Table II), but that total ^{31}P signal is reduced. Such studies require absolute quantification of metabolite concentrations. This is difficult in brain, for, unlike muscle MRS studies (Griffiths & Edwards, 1988), the validity of MRS metabolic concentrations can only in rare circumstances be checked by comparison with alternative biochemical quantification of a sample obtained by a needle biopsy. Alternative sources of referencing must therefore be sought. Several methods have been suggested (Tofts & Wray, 1987, 1988). All rely on assumptions of some sort.

In any study where absolute concentrations are to be measured, it is important to compensate for saturation effects. Each metabolite is affected differently by saturation, so the peak area of each metabolite in a spectrum must therefore be corrected by a constant (saturation factor) for that peak (Cady & Azzopardi, 1989; Weiner *et al*, 1989). In practice saturation factors are determined for normal volunteers and it is assumed that the T_1 relaxation constants of the different metabolites do not alter significantly between normal and abnormal states (Weiner *et al*, 1989). There is evidence to suggest that this assumption may not hold in some organic states.

Several studies have recently been published in which absolute metabolic concentrations in brain were measured (Cady & Azzopardi, 1989; Weiner *et al*, 1989; Bottomley, 1989). Intra-individual variations of 5–15% standard deviation of the mean have been quoted for absolute metabolite concentrations (Buchtal *et al*, 1989) in muscle and liver using ID–CSI.

Method of data processing

Processing raw MR data for the purpose of quantification has a large effect on the final appearance of a spectrum. Manual and labour-saving computerised methods for calculating spectral peak areas perform equally well, provided that certain important criteria are met with regards to computerised methods (Martin *et al*, 1988). By far the most important variable is the SNR – given that the operator is experienced in MR data processing.

Study design

Interrogative studies

Clinical MRS studies to date have relied heavily on detailed longitudinal interrogative studies of "paradigm patients" (Griffiths & Edwards, 1988).

In these studies a subject acts as his/her own control, and abnormalities in metabolism are demonstrated when the system is under stress (e.g. by muscle exercise, anoxia or ischaemia).

How can one stress the brain? Considering the practical constraints of patient positioning, it is doubtful whether psychometric stress tests could be undertaken during an MR examination. There is, however, potential for pharmacological interrogative methods.

Comparative studies

Using a patient as his/her own control has a number of advantages and is possible in some comparative studies (e.g. of tumours and strokes) where pathology is focal. The contralateral hemisphere is healthy and may be used as a control.

Most psychiatric conditions are global, or have only subtle laterality, which necessitates comparative group studies. The insensitivity and cost of MRS tools make them unsuitable for studies which need large patient and control groups to show statistically significant small changes in absolute biochemical concentrations. It is highly unlikely, considering the many sources of error and man–machine variables, that changes smaller than 15–20% will be detected between affected individuals and controls.

Protocol for an integrated examination

It must be understood that an integrated MR approach has an inherent flexibility (Griffiths & Edwards, 1988), related to the tool's versatility for examining several magnetically susceptible nuclei, combined with precise anatomical and pathological localisation of tissues of interest. Fig. 10 outlines a suggested protocol for the integrated examination of patients with early signs of dementia. This protocol, based on the comparative approach, necessitates absolute quantification of ^{31}P metabolites and assumes that findings between age-matched normal and affected individuals will be greater than 20% – the reproducibility error expected.

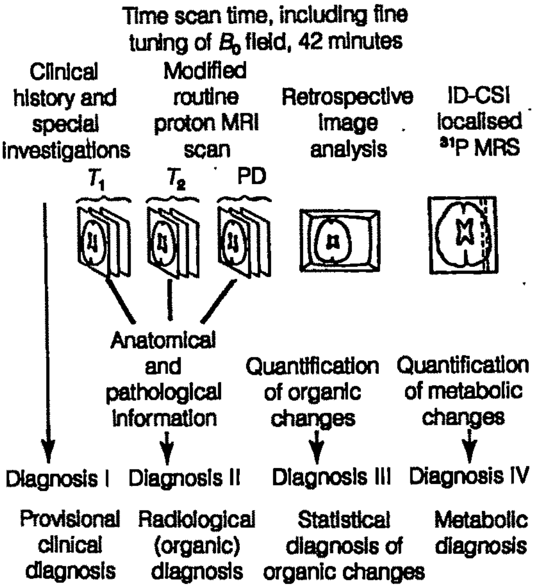
Time scan time, including fine tuning of B_0 field, 42 minutes
Clinical history and special investigations
Modified routine proton MRI scan
Retrospective image analysis
ID-CSI localised ^{31}P MRS
T_1
T_2
PD
Anatomical and pathological information
Quantification of organic changes
Quantification of metabolic changes
Diagnosis I
Diagnosis II
Diagnosis III
Diagnosis IV
Provisional clinical diagnosis
Radiological (organic) diagnosis
Statistical diagnosis of organic changes
Metabolic diagnosis

FIG. 10 Protocol: an integrated MR examination for patients with early signs of dementia (adapted from the approach recommended by the General Electric Company in their literature towards the possible integration of MRI and MRS).

Conclusions

The word 'biopsy' is taken from the Greek *bios* (meaning life) and *opsis* (meaning vision). There is no doubt that *in-vivo* MRS studies of psychiatric patients are feasible. The prize to be had from magnetic resonance is truly a 'vision of life'. The integrated MR examination is the only technique which allows us to study, non-invasively, the inter-relationship between structure, function and biochemistry in the brain.

The question is whether the information generated by MRS will facilitate the diagnosis, understanding and management of psychiatric illness. MRS is not in competition with other functional neuroimaging techniques: there are as yet few cost-effective indications or therapeutic benefits for any of the functional neuroimaging techniques in psychiatry. Retrospective automated quantitative analysis of MR images and clinical applications of MRS are extending rapidly, and our knowledge about the structural, biochemical, pharmacological and metabolic alterations in psychiatric syndromes is growing. Where will this new technology lead us? In the context of our general ignorance, the integrated MRI/MRS examination can only lead to new truths.

Magnetic resonance spectroscopy in psychiatry is in its infancy – very much a case of fishing in uncharted waters – and findings therefore require careful scrutiny in terms of the quality of the particular MRS 'fishing net' used. It is in the area of the man–machine interaction and sources of technical artefact that the focus of our MRS research is concentrated, for it is only when these variables have been standardised for a given clinical hypothesis that the MRS component of the integrated examination will have reliable face validity.

Detailed longitudinal studies of individual paradigm cases are a logical starting-point. The screening of large numbers of patients in any one centre in the hope of finding small statistically significant changes is not a cost-effective option. Relating MRS discoveries to biochemical and functional information obtained by existing clinical techniques and comparing these findings with *in-vivo* animal and *in-vitro* findings will increase the chance of understanding the underlying biological bases of psychiatric syndromes, thereby gaining clues to rational therapy.

The new era in MR technology is an opportunity that should not be missed. There is undoubtedly a high price to pay for new technology, but this price needs to be put against the certain cost of our ignorance in terms of the effect it has had and will continue to have on providing health care for our patients.

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Magnetic Resonance Imaging and Spectroscopy in Schizophrenia

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In this new era of structural and functional neuroimaging technologies, it is the unsurpassed anatomical resolution of magnetic resonance imaging (MRI) (Andreasen, 1989; and Besson, this supplement) that has resulted in a new generation of studies on cerebral morphology in schizophrenia. With the recent development of whole-body magnets of very high ($\geqslant 1.5$T) and uniform field strength, it has become possible to extend the scope of this approach to include measurement of certain fundamental neurochemical processes, via magnetic resonance spectroscopy (MRS: Hubesch *et al*, 1989; Lock *et al*, this supplement). The purpose of this article is to introduce and review critically the existing literature on the application of MRI and MRS to schizophrenia, and to give a preliminary account of some of our own recent studies in these areas.

Magnetic resonance imaging

The basic principles of MRI have been described very clearly by Andreasen (1989), and a historical perspective and detailed resumé of the range of its clinical applications in brain disorders is available (Hyman & Gorey, 1988). The inherently superior resolution of this technique for brain morphometry is being continually extended by the development of increasingly sophisticated software for image analysis (Caviness *et al*, 1989).

Interpretation of the now extensive literature on cerebral structural pathology in schizophrenia using X-ray computerised tomography (CT) has been hampered by its limited anatomical resolution; the debate has centred on lateral ventricular enlargement, but has encompassed other phenomena, including enlargement of the cortical sulci and abnormalities in hemispheric asymmetry (Shelton *et al*, 1988; Lewis, this supplement). The increased soft-tissue contrast and discrimination of MRI, compared with CT, as well as improved spatial resolution, has resulted in enhanced anatomical definition. The absence of bone and some metal artefacts (e.g. dental amalgam), together with the multiplanar facility, enables the brain to be imaged to considerable advantage. Thus MRI lends itself readily to elucidating the basis of the non-specific changes noted above, and to identifying more localised structural abnormalities by way of quantitative *in-vivo* morphometry.

Quantitative structural imaging

Quantitative MRI studies of cerebral structure in schizophrenia are summarised in Table I. Of the seven studies that have investigated lateral ventricular size/ventricular brain ratio, four have reported enlarged ventricles while three have not; it should be emphasised that by no means all CT studies have produced positive findings (Shelton *et al*, 1988). In relation to MRI, the ability to derive multiple contiguous sections through the extent of the ventricles allows computation not only of their area in a given section but also their volume. Among the three studies that have carried out this potentially much more informative analysis, each has reported an increase in lateral ventricular volume; in one of these, such volumetric enlargement appeared to be confined to males.

Regarding the negative findings on area measures, the nature of the control population selected for such studies has recently received considerable attention. In the CT literature, a debate has endured as to whether 'normal' volunteer controls may show larger ventricles than medical controls scanned for a possible disorder but judged to be 'normal' on neuroradiological evaluation; the debate revolves around whether this judgement might exclude controls with ventricles at the upper end of the normal distribution and thus bias the sample towards a lower mean (Smith *et al*, 1988; but see Raz *et al*, 1988). It should be noted that in two recent MRI studies, a not insignificant number of normal volunteer controls were found to have relatively large ventricles (Andreasen *et al*, 1990; Olson *et al*, 1990; see also present study, below) and volunteer controls may have an unexpectedly high frequency of a personal and/or family history of psychiatric disorder (Halbreich *et al*, 1989; Olson *et al*, 1990).

It is apparent from Table I that the results of MRI studies on the corpus callosum in schizophrenia are highly inconsistent. This may in part reflect the

TABLE I

Controlled, quantitative studies of cerebral morphology in schizophrenia by MRI

Study	*Subjects*		*Age:*[1] *years*	*MRI parameters*[2]		*Results*[3]
	Controls	*Patients*		*Plane(s)*	*Sequence(s)*	
Smith *et al* (1984)	5	9	27.4±7.9	A,S,C	SE,IR (0.3T)	NS: VBR and CC:brain ratios
Mathew & Partain (1985)	12	12	35.0±8.8	S	SE (0.5T)	NS: cerebellar vermis and 4th ventricle
Mathew *et al* (1985)	18	18	38.4±14.0	S	SE (0.5T)	↑ septum pellucidum and CC length NS: cerebral and CC areas
Andreasen *et al* (1986)	49	38	33.2±8.2	S,C	IR (0.5T)	↓ frontal, cerebral and cranial areas
Nasrallah *et al* (1986)	41	38	33.2±8.2	S	IR (0.5T)	↑ CC area but not length ↓ CC width in females
Smith *et al* (1987)	21	29	30.7±8.0	A,S,C	SE,IR (0.3T)	NS: VBR, 3rd ventricle and sulcal width NS: CC:brain height and ratio
DeLisi *et al* (1988)	18	24	31.9±7.0	C	? (0.5T)	↓ temporolimbic complex
Kelsoe *et al* (1988)	14	27	29.0±5.2	S,C	IR (0.5T)	↑ VBR, 3rd ventricle and ventricular volume NS: cerebral, frontal and temporal volumes NS: multiple indices of CC
Uematsu & Kaiya (1988*a*,*b*)	17	40	32.2±6.7	S	IR (0.5T)	↑ anterior CC:brain ratio NS: multiple other indices of CC NS: cerebral area and cerebellum:brain ratio
DeMyer *et al* (1988)	24	24	28.7±6.6	A	SE,IR (0.15T)	↓ left frontal area
Rossi *et al* (1988*a*, 1989*a*)	15	15	33.2 (19–47)	A,S	SE (0.5T)	↑ VBR ↓ CC:brain ratio but not CC length
Stratta *et al* (1989)	20	20	32.3±6.3	A,S	SE (0.5T)	↓ left v. right frontal width
Suddath *et al* (1989)	17	17	30.6±6.5	C	IR (0.5T)	↓ temporal-lobe grey-matter volume ↑ ventricular volume but not frontal volume
Johnstone *et al* (1989)	21	21	35.9 (26–48)	C	SE (0.15T)	NS: ventricular size, brain and temporal lobe ↑ temporal-horn size in males
Rossi *et al* (1989*b*)	11	15	26.7±4.9	C	SE (0.5T)	↓ temporal-lobe area, especially on left
Hauser *et al* (1989)	25	24	33.0±9.3	S	SE (0.5T)	NS: multiple indices of CC
Andreasen *et al* (1990)	47	54	33.4±9.3	S,C	IR (0.5T)	NS: frontal cerebral and cranial areas, CC, cingulate gyrus, cerebellum, parietal and occipital lobes ↑ ventricular volume in males ↓ thalamic area in males

1. Age as mean and s.d. or range.
2. A = axial (transverse); S = sagittal; C = coronal; SE = spin–echo; IR = inversion–recovery; T = magnetic field strength in teslas.
3. Results are area or linear measures, unless otherwise stated. NS = not significant; ↑ = increase; ↓ = decrease. CC = corpus callosum; VBR = ventricle : brain ratio.

considerable range of general variations in human callosal size and shape (McLeod *et al*, 1987) and the wide range of measurement procedures adopted; as intrinsic intersubject differences in callosal structure appear to be of greater magnitude than those associated with age, sex, brain size or handedness (Kertesz *et al*, 1987; Byne *et al*, 1988), such differences would also tend to obscure any that might be associated specifically with schizophrenia. Furthermore, measurement of callosal morphology, or of any other cerebral region(s) displayed on mid-sagittal images, may be prone to artefacts of slice position and thickness (Coffman *et al*, 1989).

In one of the most detailed of the initial MRI studies, Andreasen *et al* (1986) reported reductions in frontal-lobe area and in cerebral and cranial size, particularly in males. However, Kelsoe *et al* (1988) and Andreasen *et al* (1990) were unable to replicate these findings, using volumetric and similar area measures respectively. The principal difference between the two studies of Andreasen *et al* (1986, 1990) appears to reside in the relevant control groups. In the initial investigation controls were clearly economically and educationally advantaged in comparison with patients, while in the subsequent study patients and controls were of similar educational backgrounds. A possible association between cerebral structure and educational attainment is suggested by the smaller frontal and cerebral areas of the latter control group, when compared with that investigated originally. The importance of examining controls who are matched educationally with patients, and the potential difficulties of not so doing, are emphasised further by the study of DeMyer *et al* (1988), who reported overall reductions in right hemisphere and both left and right frontal area in schizophrenia; on controlling for educational level, only the reduction in left frontal area remained significant.

Regarding more circumscribed regions, DeLisi *et al* (1988) reported reduced area of a temporal lobe complex of hippocampus/amygdala and parahippocampal gyrus. While Kelsoe *et al* (1988) did not note any differences either in temporal lobe or in hippocampus-amygdala volume, this group (Suddath *et al*, 1989) did report subsequently a reduced volume of temporal-lobe grey but not white matter, particularly in sections containing the amygdala and anterior hippocampus. Similarly, Johnstone *et al* (1989) reported a tendency for temporal-lobe area to be reduced; more prominently, while the right temporal lobe appeared smaller in controls, this pattern of asymmetry was reversed in schizophrenia, and male patients showed significantly enlarged temporal horns. Reduced temporal-lobe area, particularly in the left hemisphere, was reported by Rossi *et al* (1987*b*). There is thus an emerging body of evidence for structural abnormalities in the (left?) temporal lobe in schizophrenia, and in one study (Suddath *et al*, 1989), temporal-lobe volume appeared to be inversely correlated with lateral ventricular size; the focus on the hippocampus/parahippocampal gyrus/amygdala region complements that emerging in recent neuropathological studies (see Jeste & Lohr, 1989), and will be facilitated by the increasing sophistication of MRI techniques for resolving these and other temporal-lobe structures (Jack *et al*, 1989).

Quantitative MR parameters

Some imaging studies have additionally made preliminary measures of regional signal intensity values, but with variable results. Smith *et al* (1984, 1987) reported increased intensity values for grey and white matter in cortical and temporal-lobe regions of schizophrenic patients. However, Kelsoe *et al* (1988) found no differences in intensity values in the pre-frontal or temporal lobe, or in the basal ganglia. While Rossi *et al* (1988*b*) also found no differences in frontal or temporal intensity values between patients and controls, they noted more left–right differences in the patient group.

Regarding regional spin–lattice relaxation time (T_1) and spin–spin relaxation time (T_2), Besson *et al* (1987) found this parameter not to differ between patients and controls in several brain regions, or between patients with and without dilatation of the lateral ventricles as determined by qualitative assessment; however, T_1 was increased in the basal ganglia of those patients with as opposed to those without tardive dyskinesia. Conversely, Andreasen *et al* (1989) have reported increased T_1 in the left striatum and increased T_2 in the left temporal white matter and the left dorsolateral grey matter. It should be emphasised that a better understanding of the measurement and physiological significance of signal intensity values and of T_1 and T_2 is only now emerging; this may well aid the interpretation of these preliminary forays.

Qualitative MRI findings in schizophrenia

The studies reviewed above have involved particular quantitative measures of selected, circumscribed brain regions that have been imaged in a single plane and using in the main a single MR sequence. While the rigor of these morphometric approaches is fundamental to the study of cerebral structure in schizophrenia, such investigations have rarely included consideration of qualitative abnormalities

TABLE II

Qualitative structural findings on cerebral MRI

Controls		*Patients*	
Age/sex		*Age/sex*	
32M	Mild lateral ventricular dilatation	53M	Generalised cerebral atrophy, with ventricular dilatation; relative sparing of cerebellum
40M	Small cavum septum pellucidum	31F	Minor cerebellar atrophy, particularly of the vermis; mild 4th-ventricular dilatation
48M	Focal area of dilatation of right temporal horn; right temporal lobe unremarkable	58F	Marked cerebral atrophy; partial agenesis of corpus callosum
59F	Mild lateral ventricular dilatation	39M	Minor atrophy of parietal cortex bilaterally
		54F	Mild lateral ventricular dilatation
		24M	Asymmetric dilatation of left lateral ventricle
		37F	Asymmetric dilatation of posterior horn of left lateral ventricle
		55F	Minor atrophy of frontoparietal region, more pronounced in left hemisphere
		62M	Generalised cerebral atrophy, with ventricular dilatation and multiple white-matter lesions
		61F	Minimal cerebral atrophy, with extensive focal and diffuse white-matter lesions, particularly in parietal region
		52M	Minor cerebral atrophy with mild dilatation of lateral ventricles
		21M	Slight cortical atrophy, particularly of frontoparietal and temporal regions
		40F	Minor cerebral atrophy of parietal lobes, bilaterally
		26M	Cerebellar atrophy (hypoplasia), with increased dimensions of 4th ventricle
		65F	Cerebral atrophy

that might be apparent on examination of the whole brain. Multiplanar imaging employing more than one sequence is required to ensure optimal visualisation of pathological processes. To extend MRI studies into this arena, we give here a preliminary account of qualitative findings from an extensive, controlled study in schizophrenia.

Patients and MRI procedures

The subjects of this study were 47 patients (26 male, 21 female; mean age 35.3 ± 12.3, range 21–65 years; mean duration of illness 12.3 ± 9.3 years) attending the out-patient clinic or day centre of St John of God Psychiatric Services, Co. Dublin, who satisfied DSM-III criteria (American Psychiatric Association, 1980) for a diagnosis of schizophrenia and gave written, informed consent to MRI. Control subjects were 25 volunteers (15 male, 10 female; mean age 34.4 ± 11.5, range 19–64 years), who had no known personal or family history of central nervous system disorder and consented similarly to MRI. This study was approved by the Ethical Committee of Cluain Mhuire Family Centre.

For MRI examination, a 1.5T whole-body Siemens Magnetom (O'Callaghan *et al*, 1988) was employed. Images were obtained in three orthogonal planes, using the following sequence parameters to demonstrate differing aspects of tissue contrast behaviour and pathology: (a) ten coronal cuts using a T_1-weighted spin–echo single multislice sequence (TR = 0.5 s; TE = 17 ms, NEX = 4; slice thickness = 4 mm), centred on the optic chiasm, with an interslice distance of 2 mm; (b) three coronal cuts using a T_1-weighted inversion–recovery sequence (TR = 1.9 s; TE = 28 ms; Ti = 500 ms; NEX = 1; slice thickness = 5 mm), centred on the basal ganglia, with an interslice distance of 5 mm; (c) 15 contiguous axial cuts using a proton-density and T_2-weighted spin–echo (double echo) sequence (TR = 3.0 s; TE = 30 and 90 ms; NEX = 1; slice thickness = 6 mm), beginning just below the vertex; (d) three sagittal cuts using a T_1-weighted spin–echo sequence (TR = 0.5 s; TE = 28 ms; NEX = 4; slice thickness = 4 mm), centred on the midline.

Images were evaluated by a consultant neuroradiologist with extensive experience in the interpretation of such material, and who was 'blind' to the status of each subject, before proceeding to quantitative analysis.

Results

Morphological abnormalities were noted in 4 of 25 controls and 15 of 47 patients (Table II). In two instances, the oldest

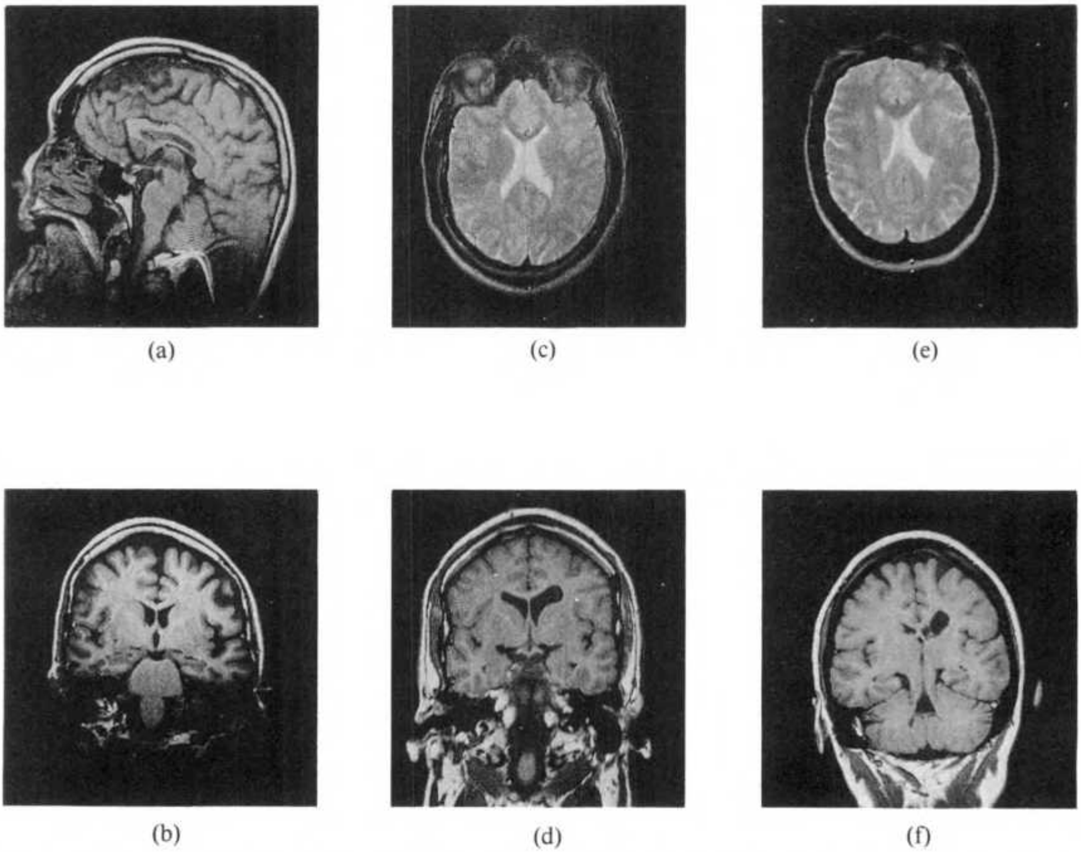

FIG. 1 (a) Mid-sagittal and (b) coronal images of 58-year-old woman with partial agenesis of corpus callosum and cerebral atrophy. (c) Axial and (d) coronal images of 24-year-old man with asymmetric dilatation of left lateral ventricle. (e) Axial and (f) coronal images of 37-year-old woman with asymmetric dilatation of posterior horn of left lateral ventricle (porencephaly).

control subject and the oldest patient, these findings were qualified as 'normal for age' and were therefore considered unremarkable. On this basis, cerebral and/or cerebellar atrophy was present in 23% of patients but absent in controls ($P<0.01$), while dilatation of the body of the lateral ventricles and/or of the fourth ventricle was present in 17% of patients v. 4% of controls; either or both such findings were present in 30% of patients v. 4% of controls ($P<0.02$).

The cerebral atrophy present in nine patients appeared generalised or diffuse in four and localised to the parietal lobes alone or involving the adjacent cortices in five, including one instance of asymmetry with the more pronounced changes in the *left* frontoparietal region. There were two patients with asymmetric dilatation of the body of the *left* lateral ventricle. Several pathological findings, all in patients, were felt to indicate neurodevelopmental anomalies: partial agenesis of the corpus callosum, asymmetric enlargement of the left lateral ventricle, and cerebellar hypoplasia; asymmetric enlargement of the left posterior lateral ventricle in a further patient suggested porencephaly of neurodevelopmental origin (Fig. 1).

Focal areas of increased signal intensity were noted in four control subjects, the periventricular region being most commonly involved, while similar high-signal foci were evident in three patients (Table III); two additional patients showed much more extensive white-matter lesions in association with morphological abnormalities (Table II).

Discussion

It is usually held, primarily on the basis of the CT literature, that abnormalities of cerebral structure in schizophrenic patients are quantitative, and that their scans would be rarely interpreted as abnormal. Nevertheless, using MRI, a consultant neuroradiologist was able to 'read' a significant excess of atrophic and lateral ventricular abnormalities among the present patient group in comparison with matched controls. However, none were felt to show serious pathological features requiring further clinical investigation, and the majority of schizophrenic brains were read as

TABLE III
Focal findings of increased signal intensity on MRI

Age/sex	*Controls*	*Age/sex*	*Patients*
48M	Discrete high signal focus in deep white matter at posterior horn of left lateral ventricle	58F	Discrete high signal foci in centrum semiovale and subcortical deep white matter
39M	Small number of high signal foci in periventricular white matter and centrum semiovale	52M	Discrete high signal foci in periventricular white matter
22F	Solitary small high signal focus in left parietal white matter	38M	Small high signal focus to the left of the central pontine area
33M	Small high signal focus at anterior horn of right lateral ventricle		

unremarkable. Among instances of generalised or localised cortical atrophy, the parietal lobes were most commonly involved, including a case with asymmetric involvement of the left hemisphere. Quantitative MRI studies in schizophrenia (Table I) have focused on the frontal and temporal lobes; though Andreasen *et al* (1990) have noted no significant findings in the parietal lobe on MRI, the CT study of Rossi *et al* (1988c) did identify highly significant enlargement of the left parietal sulcus. For all instances of asymmetric pathology in patients, the left hemisphere was the more affected; such findings are complementary to notions of left-hemisphere dysfunction in schizophrenia (Crow, 1986; Takahashi *et al*, 1987).

The term 'atrophy' has been used here in accordance with conventional neuroradiological parlance. However, current perspectives of schizophrenia posit a neurodevelopmental disorder, with abnormalities in brain morphology reflecting not cerebral deterioration but rather a failure to attain subtle but fundamental aspects of cerebral structure and function because of aetiological events acting early in embryonic/foetal life (Weinberger, 1987; Murray & Lewis, 1987; Lyon *et al*, 1989; Waddington, 1990). We noted no systematic relationship between the presence of enlarged cortical sulci and of lateral ventricular enlargement; this might be consistent with the recent study of Cannon *et al* (1989), who reported "multisite developmental deficits" in cortical morphology and ventricular abnormalities to be separate dimensions of pathology with bases in genetic and obstetric factors, respectively.

More specifically, we found several instances of putative neurodevelopmental anomalies in cerebral structure among our schizophrenic patients. The case of partial agenesis of the corpus callosum in schizophrenia complements two other cases in the literature (Lewis *et al*, 1988; Andreasen *et al*, 1990). Callosal agenesis usually occurs with other cerebral malformations, including the gyral/sulcal abnormalities noted in the present case; such dysplasia is believed to reflect events which occur between the 5th and 17th week of gestation and has been noted to have some relationship to genetically determined metabolic disorders such as hyperglycinaemia (Kolodny, 1989). A putative instance of cerebellar hypoplasia is perhaps less informative on the timing and nature of dysplastic events (Friede, 1975). The development of asymmetric enlargement of the left lateral ventricle in two patients is striking. If at least one of these cases is porencephaly, its neurodevelopmental origin is evidenced neuropathologically by such cavities having smooth walls with minimal scarring and by developmental disturbances in the cytoarchitecture of adjoining cortex (Friede, 1975). Although other structural abnormalities appeared more common in older schizophrenic patients, this also need not indicate neurodegenerative disease; we have argued (Waddington *et al*, 1988) that neurodevelopmental abnormalities may render certain structures more vulnerable to the effects of advancing age, and this may masquerade as 'progression'.

We could find no evidence that focal areas of signal hyperintensity on MRI ('unidentified bright objects') were more common in the periventricular or other regions of the brain in schizophrenia; this confirms in more chronically ill patients the initial report of Johnstone *et al* (1986) in first-episode patients. Although such phenomena may reflect small deep plaques of demyelination, subclinical infarction or atherosclerotic change in deep perforating arteries, they have been recognised in otherwise normal, asymptomatic individuals; thus, the clinical significance of isolated, focal findings is at present unclear (Sarpel *et al*, 1987; Kertesz *et al*, 1988). A very recent study has reported an excess of subcortical signal hyperintensities in some 50% of patients with bipolar affective disorder, which were static on follow-up over one year; they appeared to be associated with more frequent hospital admissions and greater cognitive deficit (Dupont *et al*, 1990).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a primary tool in chemistry which can provide information on the concentrations of endogenous substances which contain naturally occurring paramagnetic nuclei such as hydrogen-1 and phosphorus-31 (Budinger & Lauterbur, 1984; Lock *et al*, this supplement). Shulman (1983) has given a good introduction to the principles of MRS, while Lenkinski (1989) presents a state-of-the-art review of clinical MRS and its associated technological complexities. MRS with ^{31}P, which has to date received the widest application in relation to brain function, can detect non-invasively the relative tissue concentrations of certain phosphorus metabolites, including those involved in energy and phospholipid metabolism. Recent applications of ^{31}P MRS have included the study of variations in ^{31}P metabolites with development of the human brain during post-natal life (Boesch *et al*, 1989), and in neurological disorders in adult patients (Oberhaensli *et al*, 1986; Heindel *et al*, 1988). A typical ^{31}P spectrum in the human brain (Fig. 2) illustrates resolution of spectral peaks for phosphodiesters (PDE), inorganic phosphate (Pi), phosphomonoesters (PME), phosphocreatine (PCr), and nucleotide triphosphates (γ-, α-, β-NTP). PCr and NTP peaks represent high-energy phosphates, while PME and PDE peaks reflect precursors of cell membrane formation and degradation, respectively; thus, the PCr:Pi ratio provides a measure of the energy status of cerebral tissue, and the PME:PDE ratio may reflect turnover of neuronal cell membranes.

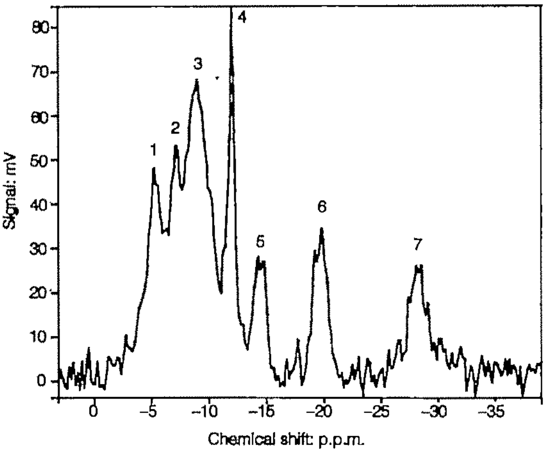

FIG. 2 ^{31}P spectrum of left temporoparietal tissue. Peaks: 1 = PME; 2 = Pi; 3 = PDE; 4 = PCr; 5 = γ-NTP; 6 = α-NTP; 7 = β-NTP.

Only two preliminary accounts of the application of ^{31}P MRS to schizophrenia are so far available. Kershavan *et al* (1989) reported on ^{31}P MRS of the pre-frontal cortex of eight heterogeneous patients with a first episode of psychosis, in comparison with ten normal volunteer controls. At entry to the study, patients showed decreased levels of PME and α-NTP, and increased levels of PDE and PCr, which endured or became greater during four weeks of neuroleptic treatment. They interpret these findings as suggesting accelerated metabolic breakdown of membrane phospholipids and decreased utilisation of labile high-energy phosphates in the pre-frontal cortex, which may parallel other indices of putative 'hypofrontality' in schizophrenia (Waddington, 1990).

Our own studies (O'Callaghan *et al*, 1989) have involved ^{31}P MRS of the left temporoparietal region of 12 chronically ill schizophrenic out-patients, in comparison with nine normal volunteer controls. We found no differences in any of the ^{31}P spectral peaks indicated in Fig. 2, or in ratios thereof. However, on deriving intracellular temporoparietal pH, in terms of the chemical shift between PCr and Pi peaks, this was found to be higher in the schizophrenic group. It may be relevant to reconsider here some of the previously discussed perspectives of putative temporal-lobe pathology and of neurodevelopmental abnormality in schizophrenia. Elevations in brain pH have been previously reported to characterise dysplastic processes, both in infants who have experienced perinatal difficulties (Laptook *et al*, 1989) and in adults with cerebral malignancies (Oberhaensli *et al*, 1986; Heindel *et al*, 1988). Indeed, Laptook *et al* (1989) have argued that pH may be a more selective marker for early tissue injury than phosphorylated energy metabolites. However, such discussion must be regarded as speculative in the absence of greater robustness in the finding, and of detailed information on any influence of neuroleptic drugs on brain pH.

Though ^{31}P and to a lesser extent ^{1}H remain the paramagnetic nuclei exploited most extensively in clinical MRS, the potential of the technique may be broader. Fluorine-19 is also a naturally occurring paramagnetic nucleus, and is present in several fluorinated neuroleptics such as fluphenazine and flupenthixol. Several pre-clinical studies have established the feasibility of ^{19}F MRS of such drugs (Bartels *et al*, 1986; Arndt *et al*, 1988; Lock *et al*, this supplement) and this holds out the promise of *in-vivo* MR spectroscopic determination of their pharmacokinetics and the imaging of their regional binding, as an alternative to positron-emission tomography (Waddington, 1989).

Conclusion

The impact on schizophrenia research of the anatomical resolution attainable with MRI has already been substantial, and its potential for *in-vivo* quantitative morphometrics is being continually extended by the increasing sophistication of software for image analysis. Its capacity for multiplanar imaging, and the range of MR sequences available to reveal differing aspects of tissue contrast behaviour and tissue pathology, are important additional advances. Critically, the absence of exposure to radiation allows for prospective studies, whereby first-episode patients might be regularly re-examined to clarify the nature of any changes in cerebral structure over the course of the illness. However, it is the very precision of such measures that can itself bring previously unappreciated problems: subtle morphological correlates of the often diverse levels of educational attainment of schizophrenic patients versus controls, and the extent of the 'normal' range for structural measures in volunteer control groups, are two examples that have emerged to date – there are likely to be others. Certainly, quantitative findings to date have been heterogeneous, and the qualitative findings diverse, with perhaps some emerging focus on the temporal lobe. The ability to make functional neurochemical measures by MRS has yet to be fully exploited. Initial procedures have usually involved averaging the sum of MR signals from *all* areas within a volume of tissue located within the sensitive region of the surface coil. Until sensitivity and methods of spectral localisation become more reliable, MRS cannot identify abnormalities of a subpopulation of neurons, or of a more circumscribed brain region. Fortunately, such developments are already well advanced, and hold considerable promise for the next generation of studies.

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The Use and Applications of Single-Photon Emission Computerised Tomography in Dementia

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The introduction of single-photon emission computerised tomography (SPECT) has markedly enhanced the study of brain function. The development of SPECT was the culmination of a series of investigations of cerebral blood flow (CBF) pioneered by Kety and Schmidt in the late 1940s combined with the introduction of transmission computerised tomography (CT) in the early 1960s, in which three-dimensional images are derived from two-dimensional data. Positron-emission tomography (PET), in addition to providing information on cerebral blood flow, also allows the evaluation of brain metabolism and neurotransmitter receptor function. However, the technology required for PET is expensive and sophisticated, with little prospect for general clinical application. Fortunately, SPECT is relatively cheap and is widely available for clinical use. We aim to review the principles and basic techniques of SPECT, its present utility and application to clinical practice, and its future potential in the investigation of brain function.

Principles and techniques

Kety & Schmidt (1948) pioneered CBF studies in man using nitrous oxide as a diffusible agent. These early studies required inhalation of nitrous oxide and sampling of arterial and internal jugular venous blood and could only provide a measure of whole-brain blood flow. Techniques to measure regional cerebral blood flow (rCBF) followed and used freely diffusible radionuclides such as krypton-85 and xenon-133, which were injected into the carotid artery (Lassen & Ingvar, 1963). Xenon-133 emits gamma radiation which can be detected through the intact skull, and multiple scintillation probes allow the measurement of CBF in specific regions of the brain. Further technological advances in detector sensitivity and data analysis allowed the replacement of intra-arterial injections by intravenous infusions or inhalation of gaseous ^{133}Xe, so that the measurement of rCBF became a non-invasive procedure. The rCBF data were initially presented in two dimensions and essentially reflected cortical flow, but with the development of the tomographic technology for SPECT, a three-dimensional measurement of rCBF could be obtained. The radiotracers used in SPECT emit a single gamma ray (or photon), as opposed to the dual simultaneous gamma rays of PET radiotracers, and hence the term 'single-photon'.

Recently, new radiotracers labelled with iodine-123 and technetium-99m have been introduced. These lipophilic radiopharmaceuticals cross the blood–brain barrier and distribute in proportion to the rCBF shortly after intravenous injection. They are trapped in the brain and have a stable or static distribution over time, unlike freely diffusible, dynamic radiotracers such as ^{133}Xe, enabling images of higher resolution to be obtained. These agents can be used with the conventional rotating gamma cameras that are widely available in most nuclear medicine departments, whereas ^{133}Xe-labelled agents cannot. The most advanced SPECT systems are now capable of a resolution of 8 mm and imaging times as short as two to three minutes for rCBF.

Unlike PET, there is no current prospect of SPECT being able to provide a direct measure of regional cerebral metabolism, but its use to measure neurotransmitter receptors is an evolving technique. The radioligand ^{123}I-3-quinuclidinyl 4-iodobenzilate (QNB) has been developed for the measurement of muscarinic acetylcholine receptors and has been applied in the study of Alzheimer's disease (Holman *et al*, 1985).

Normal subjects and normal ageing

Devous (1989) has reviewed the numerous studies of CBF in normal subjects. The early studies of whole-brain CBF, using the inert-gas washout technique, calculated flow rates of 50–60 ml/min/100 g. Later studies have found similar rates and have shown that grey-matter rCBF is approximately four times higher than that of white matter. Two-dimensional studies of rCBF, using ^{133}Xe, have reported a pattern of highest flow in the frontal lobes, but this has not been found in tomographic studies, suggesting that the hyperfrontality of two-dimensional studies is the result of a technical artefact. Dynamic tomographic studies with ^{133}Xe produce similar values for grey-matter flows as found with PET, but substantially overestimate white-matter rCBF and consequently give a limited distinction between grey and white matter. Static tomographic studies with ^{123}I- and ^{99}Tc^{m}-labelled radiotracers cannot, as yet, provide an absolute measure of rCBF, but the pattern of rCBF, which can be expressed semiquantitatively, is similar to that found in PET studies, and the resolution is better than with ^{133}Xe dynamic tomographic studies.

The pattern of rCBF reported in normal subjects reflects, at least in part, the conditions of the subjects at the time. For example, if subjects are studied with eyes open the visual cortex has the highest individual rCBF, but if the eyes are closed the rCBF is reduced (Devous, 1989). At present there are no generally accepted standard conditions for the control or resting state but it is clear that these should be standardised in any individual study.

Initial studies of the whole brain found a reduction in CBF and cerebral metabolic rate of oxygen with age (Kety, 1956). This prompted the National Institute of Mental Health (NIMH) to examine a rigorously selected population of healthy subjects in the community (Dastur *et al*, 1963). The study revealed no change in CBF or oxygen consumption, but a significant decrease in cerebral glucose consumption with age. Subsequent studies have, however, generally confirmed that CBF does fall slightly with age (McGeer, 1986). The subjects selected by Dastur *et al* (1963) were unusually healthy and even they had a trend to reduced CBF. They also found that asymptomatic elderly subjects with atherosclerosis or hypertension had significantly reduced CBF, although the cerebral metabolic rate of oxygen was not reduced to a similar level (Dastur, 1985). An extensive cross-sectional and longitudinal study by Shaw *et al* (1984) found reduced CBF in relation to both advancing age and progressive cerebrovascular disease; the researchers concluded that hypertension was the most important predisposing factor for a significant reduction in CBF.

The reduction in rCBF with age is confined to the grey matter – the white matter is unaffected (Frackowiak *et al*, 1980; Lebrun-Grandie *et al*, 1983). It has been reported to be more marked in anterior cortical regions (Hagstadius & Risberg, 1989), but others believe that the changes of ageing are generalised (Frackowiak *et al*, 1984). Females have higher rCBF than males for subjects up to 60 years of age (Devous *et al*, 1986) but the difference lessens over this age (Shaw *et al*, 1984).

Studies using PET have found that the reduction in CBF which occurs in normal ageing is not matched by an equivalent fall in cerebral metabolic rate of oxygen, suggesting increasing oxygen extraction with age (Lebrun-Grandie *et al*, 1983; Frackiowiak *et al* 1984). The PET studies of regional cerebral metabolic rate of glucose in relation to age have been contradictory. Kuhl *et al* (1982*a*) found a reduced glucose metabolic rate in the elderly, but this has not been confirmed by De Leon *et al* (1983) or Duara *et al* (1984).

Activation studies

Two-dimensional and tomographic techniques to study rCBF and regional cerebral metabolism have been used to study brain function in relation to sensory, motor, cognitive and pharmacological activation. A number of PET studies have demonstrated that sensory stimulation is associated with increased rCBF or metabolism, with area-specific activation, depending on the sensory modality stimulated (Holcomb *et al*, 1989). SPECT has demonstrated increased rCBF in the visual cortex in response to visual stimulation (Devous, 1989). Cognitive-activation studies have shown generalised or discrete increases in rCBF and metabolism depending on the cognitive tasks. For example, two-dimensional rCBF techniques have shown that the left posterior inferior frontal region (Broca's area) has increased rCBF during speech, while the posterior region of the right hemisphere has increased flow during visuospatial problem solving (Devous, 1989). SPECT studies of rCBF in response to cognitive activation have also shown discrete increases in flow which are related to the given task (Podreka *et al*, 1987; Devous, 1989). Pharmacological challenge studies using PET and SPECT have recently been undertaken by stimulating specific neurotransmitter systems and monitoring rCBF or metabolism (Wolkin *et al*, 1987; Geaney *et al*, 1990).

In the normal brain under resting conditions, energy is provided almost entirely by the oxidative metabolism of glucose, and over 90% of glucose metabolism occurs by oxidation (Siesjo, 1978). Thus, in the normal individual at rest, the rCBF is closely coupled to the regional metabolism of glucose and oxygen and is felt to reflect the underlying cerebral function (Raichle *et al*, 1976; Lebrun-Grandie *et al*, 1983). PET studies have shown that during visual stimulation, the rCBF and metabolic rate of glucose have similar marked focal increases in the visual cortex, while the regional cerebral metabolic rate of oxygen has a much smaller increase (Fox *et al*, 1988). This uncoupling of glucose uptake and oxygen metabolism suggests that most of the extra glucose taken up during physiological stimulation is not oxidised and presumably lactate production by glycolysis increases. The implication of these findings is that in normal resting individuals, rCBF and the regional cerebral metabolic rate of oxygen or glucose will provide similar information about the underlying cerebral function, but when physiologically (or perhaps pharmacologically) stimulated, they may convey information about different aspects of cerebral function, with none being automatically considered to be the most relevant index of cerebral function. Similarly, in pathological cerebral conditions, close coupling of rCBF and the cerebral metabolic rates of glucose and oxygen cannot automatically be presumed to be retained.

Studies in dementia

In addition to the effects of normal ageing, functional imaging studies in dementia have three further problems: (a) the normal variation in measures of cerebral blood flow or metabolism; (b) uncertainty of diagnosis of type of dementia (e.g. Alzheimer's disease (AD) or multi-infarct dementia (MID)) – AD accounts for over 50% of cases, and can only be diagnosed definitively by cerebral biopsy or at autopsy; (c) the presence of cerebral atrophy. Brain atrophy occurs with ageing in normal individuals and is greater in severity in patients with dementia than age-matched controls (Jacoby & Levy, 1980). However, some demented individuals have little atrophy while some normals show considerable atrophy. Consequently areas of apparently reduced rCBF in patients with dementia may be due to reduced flow to a normal volume of brain, normal flow to a reduced volume of brain or reduced flow to a reduced volume of brain.

The studies by Kety and Schmidt indicated lower rates of mean CBF in patients with dementia than in normal subjects, and most subsequent studies have confirmed these findings. Whole-brain studies have suggested that coupling between CBF and the cerebral metabolic rates of oxygen and glucose is present in the later stages of dementia, and though the link between CBF and the metabolic rate of oxygen is apparent in the early stages also, the metabolic rate of glucose is dissociated from these such that it is relatively decreased in AD but increased in MID (Hoyer, 1982).

Studies using PET have been able to make regional measurements of oxygen and glucose metabolism, in addition to rCBF, in dementia. In AD, whichever index of cerebral activity is measured, the studies demonstrate a similar pattern of regional pathology, which is characteristically bilateral in the posterior temporal and parietal regions in the early stages, and later affects the frontal lobes. White matter as well as grey matter is affected but the primary motor, sensory and visual cortices are relatively unaffected. For example, Frackowiak *et al* (1981), using oxygen-15, reported decreased oxygen consumption in temporal and parietal areas in AD, with frontal-lobe involvement in severely affected individuals. The coupling between rCBF and the regional oxygen consumption was maintained. Studies of glucose metabolism in AD, using fluorine-18 fluorodeoxyglucose, have demonstrated similar regional deficits (Friedland *et al*, 1983; Foster *et al*, 1984; Duara *et al*, 1986). In MID, in view of the individual pattern of ischaemic damage which is not confined to specific areas, there is a variable pattern of reduced rCBF and oxygen metabolism, though these remain coupled (Frackowiak *et al*, 1981). Similarly, glucose metabolism is reduced in a focal and asymmetric manner in MID (Benson *et al*, 1983).

The PET studies in AD have confirmed that the reductions in mean CBF and oxygen and glucose metabolic rates are correlated with the degree of dementia (Frackowiak *et al*, 1981; Chase *et al*, 1984). Focal neuropsychological deficits are correlated with focal reductions in glucose metabolism, such that AD patients with disproportionately severe language impairments have focal left-hemisphere hypometabolism, those with visuospatial impairment have focal right-hemisphere hypometabolism, and those with marked personality changes or attentional deficits have prominent frontal hypometabolism (Foster *et al*, 1983; Chase *et al*, 1984; Haxby *et al*, 1985). Studies of patients with early AD suggest that the focal cortical reductions in glucose metabolic rate precede the appearance of focal neuropsychological deficits and that small further metabolic reductions are associated with marked impairment in neuropsychological function (Foster *et al*, 1984; Haxby *et al*, 1986; Grady *et al*, 1988). A reduction in the intercorrelations between glucose metabolic rates in multiple brain regions in early AD implies that there is also a breakdown of the functional interrelationships within and between hemispheres (Horwitz *et al*, 1987). The use and application of PET in dementia has been critically reviewed by Burns *et al* (1989*b*).

The use of SPECT to study dementia has been reported since the mid-1980s. Using the ^{133}Xe inhalation technique, Bonte *et al* (1986) found that out of 24 patients with probable AD, 19 had perfusion deficits which were most commonly found in the parietotemporal region bilaterally and less frequently in the frontal lobes. None of five patients with MID had bilateral deficits in parietotemporal flow but instead had a patchy distribution pattern. However, ^{133}Xe SPECT involves measuring temporal variations in activity and is only possible with purpose-built equipment. The image characteristics are relatively poor because of scatter of the low-energy gamma rays and low counts obtained over the brief scanning periods.

The radiopharmaceutical ^{123}I-iodoamphetamine (IMP) does not present these technical problems and its initial cerebral uptake is proportional to rCBF (Kuhl *et al*, 1982*b*). It was the first tracer to be widely used in static SPECT studies of dementia. These have generally reported that patients with AD have deficits in flow which are maximal bilaterally in the parietotemporal cortex while patients with MID vary from having a normal pattern to marked asymmetrical focal deficits anywhere in the cortex (Cohen *et al*, 1986; Sharp *et al*, 1986*a*; Jagust *et al*, 1987; Johnson *et al*, 1987). Sharp *et al* (1986*a*) also found that, despite having characteristic regional abnormalities on SPECT, the majority of patients with AD had a normal appearance in those regions on magnetic resonance imaging (MRI). Ebmeier *et al* (1987) found that while MRI was not able to differentiate between AD and MID, 19 out of 21 patients with AD compared with 4 out of 18 MID patients showed bilateral deficits on IMP SPECT scans. Although the distribution of ^{123}I-IMP initially reflects the rCBF, redistribution of the tracer occurs approximately one hour after injection (Creutzig *et al*, 1986). The use of ^{123}I-IMP is also limited by the restricted availability of ^{123}I, which has a half-life of 13 hours, and is costly to produce, as this requires a cyclotron.

^{99}Tc^{m}-HMPAO SPECT

Technetium-99m is readily available from commercial generators in nuclear medicine departments, is inexpensive and has a shorter half-life (six hours) and better dosimetry than ^{123}I. Labelling with ^{99}Tc^{m} is a much more complex procedure than with ^{123}I, and the development of a ^{99}Tc^{m}-labelled compound to provide a measure of rCBF was a major advance in SPECT technology, resulting from a joint research programme between Amersham International and the University of Missouri. Technetium-labelled hexamethyl propyleneamine oxime (HMPAO) is a lipophilic tracer which, after intravenous administration, crosses the blood–brain barrier with high extraction and is retained in the brain in hydrophilic form (Neirinckx *et al*, 1987, 1988). The brain uptake occurs over the first two minutes and has a stable distribution for many hours (Sharp *et al*, 1986*b*; Lassen *et al*, 1988). This enables conventional equipment to be used to detect the radiation emitted from the brain. In animals the uptake of ^{99}Tc^{m}-HMPAO is linearly related to rCBF (Lear, 1988). Comparative studies with PET in humans reveal a tendency to underestimate flow in areas of high rCBF but a good correlation with areas of low and medium rCBF (Inugami *et al*, 1988; Yonekura *et al*, 1988). Although ^{99}Tc^{m}-HMPAO cannot, at present, be used to quantify rCBF absolutely, the results can be expressed semiquantitatively by comparing the counts in each brain region of interest (ROI) to a reference area such as the whole brain or cerebellum.

A number of SPECT studies have now been performed using ^{99}TC^{m}-HMPAO to investigate dementia and the characteristics of these are shown in Table I. The studies varied in the populations studied, diagnostic criteria used and the methods of assessment of images. Plate IV shows ^{99}Tc^{m}-HMPAO scans from such studies of an elderly normal volunteer, a patient with AD, and a patient with MID. Some of these studies had no data on control subjects for comparison. The majority carried out initial screening with CT or MRI to exclude structural lesions.

The early studies used qualitative assessment of the images and found that most patients with AD had bilateral parietotemporal deficits; those who did not tended to be less impaired cognitively (Gemmell *et al*, 1987). Frontal deficits also were seen in AD. Deficits were less common in MID than AD, particularly when known infarcts on MRI were excluded, and they occurred in a more variable and asymmetrical pattern. Neary *et al* (1987) also investigated patients with progressive supranuclear palsy (PSP) and others with the clinical syndrome of dementia of frontal-lobe type (DFT) which is consistent with, although not necessarily diagnostic of, Pick's disease (Neary *et al*, 1988). They found that 14 of their 21 patients with AD had posterior hemisphere deficits which were generally (11 of the 21) bilateral and correlated with the presence of visuospatial deficits. The four AD patients with no perfusion deficits had early AD with selective memory impairment. Half of those with posterior deficits also had anterior deficits, and when the latter were bilateral they were associated with a disproportionate impairment in personal and social conduct. Selective deficits in the anterior hemisphere were found in only three of the 21 patients with AD in contrast to seven of the nine patients with DFT and seven of the eight with PSP. The pattern of the frontal deficits generally differed between DFT and PSP in that the latter had an intact rim of frontal cerebral perfusion suggesting impairment of function in the subcortical region. All patients had CT scans which revealed cerebral atrophy only and

TABLE I

^{99}Tc^{m}-HMPAO SPECT studies in dementia

Study	*Patients (n)*	*Normal controls*	*Diagnosis*	*Assessment of images*	*Results*
Neary *et al* (1987)	AD (21) DFT (9) PSP (8)	None	NINCDS–ADRDA, Hachinski, CT scan	Qualitative	AD: posterior perfusion deficits (14/21) DFT & PSP: anterior perfusion deficits (7/9, 7/8)
Gemmell *et al* (1987)	AD (17) MID (10)	3	DSM–III, Hachinski, MRI	Qualitative	Bilateral temporo-parieto-occipital perfusion deficits more common in AD (13/17) than MID (2/10)
Podreka *et al* (1987)	Dementia (12)	11	Clinical, CT scan	Qualitative	Dementia: all showed perfusion deficits
Perani *et al* (1988)	AD (16)	16	NINCDS–ADRDA, Hachinski, CT scan/MRI	Semi-quantitative (ratio of ROI to cerebellum)	Decreased rCBF in bilateral frontal and posterior temporoparietal regions
Burns *et al* (1989*a*)	AD (20)	6	NINCDS–ADRDA, CT scan, CAMCOG	Semiquantitative (ratio of ROI to cerebellum)	Decreased rCBF in bilateral temporal and posterior parietal regions; correlations with neuropsychology
Hunter *et al* (1989*a*)	AD (12) Korsakoff's psychosis (10)	12	NINCDS–ADRDA, CAMCOG	Semiquantitative (ratio of ROI to occipital region)	AD: reduced rCBF in bilateral posterior temporal and parietal regions; correlations with neuropsychology KP: normal rCBF in posterior temporal region
Goldenberg *et al* (1989)	AD (23)	None	NINCDS–ADRDA, CT scan, neuropsychology	Semiquantitative (ratio of ROI to all ROIs)	Covariation of rCBF with neuropsychology
Battistin *et al* (1989)	AD (21) Mixed (9)	None	DSM–III, Hachinski, CT scan	Semiquantitative (ratio of ROI to cerebellum); basal and activated (*L*-acetylcarnitine) studies	Lowest rCBF in parietal area; increased with LAC
Geaney *et al* (1990)	AD (8)	8	NINCDS–ADRDA, Hachinski, CAMCOG	Semiquantitative (ratio of ROI to cerebellum); basal and activated (physostigmine) studies	Reduced rCBF in bilateral posterior parietotemporal region, focally increased with physostigmine; correlations with neuropsychology
Montaldi *et al* (1990)	AD (26)	10	CAMDEX	Semiquantitative (ratio of ROI to occipital region)	Reduced rCBF in bilateral posterior temporal and frontal regions; correlations with neuropsychology
Upadhyaya *et al* (this supplement)	AD (14)	12	NINCDS–ADRDA, Hachinski, CAMCOG, GMS–AGECAT,	Qualitative and and semi-quantitative (ratio of ROI to cerebellum)	Reduced rCBF in parietal and frontal regions

could not distinguish between the three conditions.

The later studies have generally been semi-quantitative. When a rotating gamma camera has been used the whole brain is scanned and the cerebellum has usually been chosen as the reference area as it is relatively unaffected by the pathology of AD (Pearson & Powell, 1989). Also, patients with AD have a normal cerebellar metabolic rate of glucose, compared with elderly controls, on PET study (Kushner *et al*, 1987). Studies using dedicated head scanners, which acquire their data in the form of transverse tomographic slices, have not usually obtained cerebellar data, so they have used the occipital region as a reference area because the latter also appears relatively unaffected by AD (Montaldi *et al*, 1990). These studies have consistently found that patients with AD have a bilateral decrease in rCBF in the posterior temporal and parietal regions, adjacent to the occipital lobe, and sometimes the frontal lobes are affected although the basal ganglia are not (Table I). Several studies have demonstrated correlations in AD between rCBF and neuropsychological function and these have tended to be more apparent for language, praxis and global function than for memory (Burns *et al*, 1989*a*; Hunter *et al*, 1989*a*; Goldenberg *et al*, 1989; Geaney *et al*, 1990; Montaldi *et al*, 1990).

Pharmacological activation studies of the effect of central cholinergic stimulation upon rCBF in AD have recently been reported. These require paired SPECT studies, basal (after saline infusion) and activated (after infusion of cholinergic agent e.g. physostigmine). In patients with AD, the reduced rCBF in the posterior parietotemporal region in the basal scan was focally increased in the scan after the cholinergic agent (Battistin *et al*, 1989; Geaney *et al*, 1990). This effect of cholinergic stimulation did not occur in control subjects (Geaney *et al*, 1990). AD is associated with striking abnormalities in the central cholinergic system and the rCBF response to cholinergic stimulation is interpreted as evidence of a functional cholinergic deficit that is at least partly reversible.

Patients with Korsakoff's psychosis, in contrast to patients with AD, have been reported to have normal rCBF in the posterior temporal region, though there was a trend to reduced flow in the frontal region which correlated with impairment in memory and orientation (Hunter *et al*, 1989*a*). Upadhyaya *et al* (subsequent paper, this supplement) have investigated elderly depressed patients and found perfusion deficits that were similar to, but less marked than, those in patients with AD. This is an interesting finding in view of the fact that some elderly depressed patients, particularly if cognitively impaired, eventually develop dementia (Reding *et al*, 1985).

It is well established that Parkinson's disease (PD) is characterised by degeneration of dopaminergic neurons in the substantia nigra, which project to the corpus striatum. In an HMPAO SPECT study, 36 patients with PD were found, overall, to have normal rCBF in the caudate and putamen; however, those on no therapy had lower rCBF, and those on *l*-DOPA-replacement therapy had higher rCBF, in the caudate and putamen, than controls. Bilateral reductions in rCBF in the parietal region, similar to those found in AD, were also found in the patients with PD. No patients had focal lesions on CT scans. Interestingly, the parietal reductions in rCBF were more pronounced in those PD patients with cognitive impairment and those receiving chronic anticholinergic therapy. Dopamine deficiency is the main, but not the only, neurochemical deficit in PD, and these SPECT findings are consistent with the concept that AD and PD may overlap to some extent (Pizzolato *et al*, 1988). Patients with Huntington's disease (HD), characterised by chorea and progressive dementia, have been found to have reduced rCBF in the caudate nucleus that was matched by caudate atrophy on MRI. However, the size of the rCBF deficit in the SPECT study exceeded that predicted by the MRI findings (Smith *et al*, 1988).

There has been a case report of a patient with pathologically proven Creutzfeldt–Jakob disease who had strikingly reduced rCBF throughout the cortex on HMPAO SPECT study but a normal CT scan (Hunter *et al*, 1989*b*). Patients with the AIDS dementia complex have been found, with SPECT, to have multiple or focal rCBF deficits, correlating with focal signs or symptoms, while CT scans showed diffuse cerebral atrophy (Pohl *et al*, 1988).

Discussion

Studies employing SPECT or PET can reveal cerebral abnormalities when CT and MRI do not, because the latter are measures of cerebral structure while the former are measures of cerebral function. SPECT is, and is likely to remain, much more generally available than PET, but it is not currently capable of absolute quantification. This has been regarded as a deficiency, but the normal individual variation in the absolute values of rCBF and metabolic rates is such that absolute measurements are of limited value. For example, control subjects who had two PET measurements of regional cerebral glucose metabolism over 24 hours had a mean change of 7% (with individual changes of up to 22%) in whole-brain metabolism. In contrast, when the metabolism in each region was expressed as a ratio of the whole-brain metabolism, the resulting average regional changes were under 1% (Bartlett *et al*, 1988). This suggests that the proportion of the whole-brain metabolism used regionally over time is stable, although the absolute values are less so. Thus, it may be more appropriate to analyse normalised data, rather than absolute values, in activation studies that use a repeated-measures design. Also, regional deficits in mild to moderate AD may be more readily detected by analysis of normalised rather than absolute values (Cutler *et al*, 1985).

The characteristic SPECT findings in AD are bilaterally decreased rCBF in the parietal and temporal lobes adjacent to the occipital lobes, sometimes involving the frontal lobes, particularly in later cases. The primary motor, sensory and visual cortices and basal ganglia are relatively unaffected. This contrasts with typical CT findings of diffuse cerebral atrophy, although the CT scans have not generally been orientated along an axis that obtains optimum views of any focal atrophy in the hippocampus and temporal lobe (George *et al*, 1990). On careful assessment, focal features can be seen on CT scans which correlate with individual symptoms such as aggression or wandering (Burns *et al*, 1990) but the extent of the focal CT abnormalities is less than that seen on SPECT, and it appears that structural atrophy lags behind clinical deficit (George *et al*, 1990).

The diagnosis of dementia and its differentiation from other clinical syndromes, such as depression, is still primarily a clinical matter. If a structural lesion, such as a cerebral tumour, is suspected, then a structural scan such as CT is likely to be the best test for this. What then is the appropriate role of SPECT in current clinical practice in the assessment of dementia? The study by Upadhyaya *et al* (this supplement) suggests that it would be unwise to expect SPECT to assist in the differentiation of dementia from depression in the elderly because similar, albeit less marked, changes are seen in depression as in AD. It would be interesting to know if those elderly individuals who present with the clinical syndrome of depression and who have the characteristic AD abnormalities on SPECT, have a worse prognosis than those with normal SPECT scans. They might be individuals at risk of developing AD where depression has been one of the early clinical features, but much more information, including follow-up studies, is needed on this patient group to evaluate the utility of SPECT. More information is also needed on the frequency with which perfusion deficits (particularly those with a pattern similar to that in AD) are seen on visual inspection of SPECT studies in healthy, elderly controls. Patients with PD, particularly those who are cognitively impaired or receiving chronic anticholinergic treament, also may have similar SPECT abnormalities to patients with AD. Perhaps it is not surprising that there may be similarities on this measure of brain function, as there can be a degree of overlap of the clinical syndromes.

If the clinical diagnosis of dementia is made in an individual patient and it appears to be a primary degenerative dementia, the SPECT study can add weight to the clinical impression that the underlying diagnosis is that of AD or DFT or PSP. AD is most characteristically associated with posterior rCBF deficits, while DFT and PSP are strongly associated with anterior rCBF deficits and themselves have distinctive patterns. CT scans, on the other hand, are not particularly helpful in this situation (Neary *et al*, 1987). Similarly, Korsakoff's psychosis appears to be more characteristically associated with frontal rCBF deficits than posterior temporal deficits (Hunter *et al*, 1989*a*). SPECT can also assist the clinical assessment in the differentiation of AD from MID: bilateral parietotemporal deficits are strongly suggestive (but not diagnostic) of AD, although it must be remembered that AD and MID coexist in a substantial minority of cases. There is no particular single pattern of rCBF deficits seen in MID. SPECT findings vary from normal to asymmetrical deficits and theoretically MID could mimic any other pattern. However, if an asymmetrical pattern is found, affecting areas other than the parietotemporal region, it is suggestive of MID. This impression is strengthened if the rCBF deficits coincide with cerebral infarcts seen on structural imaging with CT or MRI. If a patient with relatively advanced dementia has a normal SPECT study it is unlikely to be AD and may be consistent with MID.

All these conclusions, however, must be tempered by the knowledge that our present association of SPECT (and PET) patterns with specific conditions is based on studies where clinical diagnoses of patients are made initially and are then correlated with the SPECT findings. We need follow-up studies and pathological findings at post-mortem to make more definitive assessments of the significance of specific SPECT patterns. We could also learn whether SPECT studies can help predict clinical outcome in individual cases. There is evidence from PET studies of patients with early AD that focal cortical reductions in glucose metabolism precede the appearance of focal neuropsychological deficits (Foster *et al*, 1984; Haxby *et al*, 1986, Grady *et al*, 1988). However, if the earlier whole-brain studies are correct and the metabolic rate of glucose is uncoupled from CBF in early AD such that it is decreased relative to CBF (Hoyer, 1982) and the rCBF is reduced later in the course of the disease (Rogers *et al*, 1986), SPECT might have different predictive power in comparison with PET in early AD. It is possible that patients at risk for HD may be diagnosed in the pre-symptomatic phase by the SPECT finding of reduced rCBF in the caudate nucleus (Mazziotta *et al*, 1987; Smith *et al*, 1988).

It is clear that SPECT will be used substantially in further research in AD. More significant advances in our knowledge of AD are likely to come from follow-up and activation studies. The latter would involve paired SPECT studies, basal and activated, and the activation could be cognitive or pharmacological. For paired studies, the important measure is the difference in rCBF between the two SPECT studies, which indicates the effect of activation. This avoids the problem of variation in basal values between individuals and the problem of the effect of an uncertain degree of cerebral atrophy upon rCBF. The semiquantitative measures of SPECT are adequate, and may be preferable, for this analysis. Cognitive activation studies in controls and in patients with AD would provide a better understanding of the cerebral processes involved in cognitive function in normal individuals, and knowledge about the form of disruption of these processes in disease (Miller *et al*, 1987). Pharmacological activation studies would enable direct measures of specific neurotransmitter function to be made and hence the pharmacological characterisation of disease in an individual, with implications for treatment and prognosis (Geaney *et al*, 1990).

Another promising direction for SPECT is the study of neurotransmitter receptors. The radioligand ^{123}I-QNB has been developed for the measurement of muscarinic cholinergic receptors and it has been used in the study of AD (Holman *et al*, 1988). Currently it requires a radiochemist on site to produce ^{123}I-QNB, and so it is not commercially available, but the development of radioligands for general use in receptor studies is likely to continue and may further extend the role of SPECT.

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A Study of Depression in Old Age Using Single-Photon Emission Computerised Tomography

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There is evidence to suggest that organic cerebral changes occur in elderly depressed patients. Quantitative studies of elderly depressed patients have demonstrated that they have reduced 'radio-attenuation' on computerised tomography (CT) scans and as a group resembled more closely a group of demented patients than normal controls (Jacoby *et al*, 1983). Many biochemical changes associated with ageing are similar to the pathophysiological abnormalities in depression and in dementia (Alexopoulos *et al*, 1988). These changes, coupled with the high frequency of depressive syndromes in demented patients, suggest a complex relationship between depression and dementia in old age. Mahendra (1985) has suggested that a variety of brain abnormalities can produce a spectrum of clinical manifestations, ranging from depression with minimal cognitive dysfunction at one end to dementia with minimal depression at the other.

The advent of non-invasive neuroimaging techniques such as positron-emission tomography (PET) and magnetic resonance imaging (MRI) has facilitated the study of cerebral changes in psychiatric disorders. Recently the development of the more widely available technique of single-photon emission computerised tomography (SPECT) has led to several studies of cerebral perfusion. SPECT can be provided more cheaply than PET, and provides similar information on regional cerebral blood flow (rCBF) (Johnson *et al*, 1987). A recent study using the lipophilic compound technetium-99m hexamethylpropylenamine oxime (^{99}Tc^{m}-HMPAO) has validated the use of SPECT in demonstrating distinctive patterns of impaired cerebral perfusion, corresponding with discrete neuropsychological deficits in patients with Alzheimer's disease (AD) (Burns *et al*, 1989). Hypoperfusion in the parietal region has been shown to be the most consistent finding in AD and this also showed the highest correlation with the severity of dementia (Johnson *et al*, 1988).

In contrast, studies on cerebral perfusion in depressive illness have been rather limited. Matthews *et al* (1980), using xenon-133, studied 13 patients with major depressive disorder (MDD) and reported significantly reduced flow in the left hemisphere compared with that in age-matched healthy controls. Gustafson *et al* (1981) found no difference in the cerebral blood flow in depressed patients compared with that in normal controls. Uytdenhoef *et al* (1983) reported increased flow in the left frontal lobe and decreased flow in the right posterior areas in patients with MDD. Gur *et al* (1984) measured rCBF at rest and during the performance of a verbal and spatial task in depressed patients and healthy controls. In depressed male patients there was a lower than normal flow at rest, but the flow increased to normal levels during cognitive activation.

Studies of affective disorders using SPECT (Rush *et al*, 1982) have also shown lower mean rCBF in unipolar endogenous depressions, which reversed with clinical recovery. There were also significant differences in right–left asymmetry between depressed patients and normal subjects. Devous *et al* (1984) compared the rCBF in depressed patients with that of the controls and confirmed the lower flow in the right temporal and parietal lobes in patients with unipolar endogenous depression. Sackeim *et al* (1990), using a ^{133}Xe inhalation technique, showed that regional cerebral perfusion in selective frontal, central, superior temporal and anterior parietal regions was reduced compared with that in healthy controls.

Most of the SPECT studies in depressed patients have included younger people. The exception to this was the study by Sackeim *et al* (1990), which reported on subjects with a median age of 62 years. In view of the established usefulness of SPECT in demonstrating cerebral changes in dementia, and the overlap between dementia and depression in the elderly group, we used SPECT to study three groups of subjects – elderly patients with AD, age-matched controls, and patients with MDD – to examine the changes in cerebral perfusion in elderly depressed patients and to study the relationship between rCBF and severity of symptoms.

Method

Eighteen patients fulfilling the DSM–III–R (American Psychiatric Association, 1987) criteria for major depressive disorder (MDD), 14 patients satisfying the criteria of

NINCDS–ADRDA (McKhann *et al*, 1984) for Alzheimer's disease (AD), and 12 healthy controls were studied. All subjects were right handed. The control subjects were free from serious physical illness and current or past history of mental illness. A cranial CT scan was performed in six patients with MDD and six patients with AD; some of these showed generalised cortical atrophy. The patients underwent routine laboratory screening, including full blood count, liver function tests, thyroid function tests, vitamin B12 and folate tests; the results were normal.

The subjects were assessed with the Geriatric Mental State (GMS) examination (Copeland *et al*, 1986), Mini Mental State (MMS) examination (Folstein *et al*, 1975), and Hachinski scale (Hachinski *et al*, 1975). All except seven patients with MDD were administered the Cambridge Cognitive Schedule (CAMCOG), which provides a detailed assessment of cognitive function (Roth *et al*, 1988). The findings on GMS examination were analysed with the GMS-AGECAT (Dewey & Copeland, 1986) computer program to yield psychiatric diagnosis for each subject. The depressed patients were administered the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) and the Newcastle scale for 'endogenicity' (Carney *et al*, 1965).

The subjects underwent SPECT between 1 p.m. and 3 p.m. They were administered 550 MBq of ^{99}Tc^{m}-HMPAO and were positioned beneath a large-field-of-view gamma camera (Siemens ZLC Orbiter: 75 tube). The camera rotated with the minimum possible radius around the subject's head. The camera motion, data processing and data acquisition were controlled by a Picker PCS 512 computer and Nuclear Diagnostics Tomographic software. Images were acquired for 30 seconds each at 64 angles and the total study time was approximately 45 minutes. A low-energy all-purpose (LEAP) collimator was used and images structured in a 64×64 matrix. A previously acquired 50-million-count flood study was used to correct the acquired data for camera non-uniformity.

Before full reconstruction, a single transaxial mid-brain slice was produced from which the elliptical dimensions of the head were determined. This provided the co-ordinate base for the attenuation correction of the reconstructed data. Image reconstruction was achieved by a filtered back-projection process and multiple transverse image slices were produced. The slice resolution was 64×64 pixels by 2 pixels thick, which corresponded to a voxel (volume element) of $0.625 \times 0.625 \times 1.25$ cm^3.

After reconstruction, the images in the transverse-section file were normalised and displayed sequentially on a colour monitor. Four relevant images from this file were selected and stored in a single 512×512 pixel image on hard disk for subsequent analysis. These images were visually inspected and reported upon by two authors (MC and SJG), who were blind to the clinical details of the subjects. Regions of interest (ROIs) identifying the frontal, temporal, parietal and occipital areas on the left and right sides of the brain were defined on these images and the average value of the counts in these ROIs were calculated. A ratio of the counts in these areas to the mean counts in a ROI defined over the right and left cerebellar region was used as an index of regional blood flow.

Statistical analysis

The ratios of radioactivity in the different regions of the brain were compared across the three groups by analysis of covariance (ANCOVA) using diagnostic group and gender as factors, and age as a covariate. Pearson's product-moment correlations were also calculated between the HRSD score, the Newcastle score, and the activity ratios of the depressed patients.

Results

The clinical characteristics of the patients and the controls are given in Tables I and II. The patients with MDD were older than both the control subjects and the patients with AD, but this difference was not significant. The sex ratio of the subjects in the depressed group was also different

TABLE I
Clinical characteristics of subjects

	Groups		
	MDD	*AD*	*Controls*
No. of subjects (no. of men)	18 (4)	14 (7)	12 (6)
Age range: years	66–90	54–81	58–91
Mean age (s.d.): years	77 (7.8)	72.3 (8.4)	74.7 (9.8)
MMS score			
range	20–30	6–19[1]	24–30
mean (s.d.)	27.3 (3.3)	11.9 (4.6)	29 (1.8)
CAMCOG score			
range	67–91[2]	5–63[1]	77–106
mean (s.d.)	83.1 (7.8)	34.4 (18.5)	94.5 (12.8)

1. Three patients with AD had marked aphasia, thus making their scores on MMS and CAMCOG unreliable.
2. The CAMCOG scores of seven subjects are not available.

TABLE II
Characteristics of the 18 depressed patients

Characteristic	
HDRS (17-item) score	
range	18–34
mean	25.9
s.d.	5.2
Newcastle score	
range	1–9
median	5
GMS/AGECAT diagnosis: no. of subjects	
"depressive neurosis, level 3"	5
"depressive neurosis, level 4"	4
"depressive psychosis, level 4"	9
Past history of depression: no of subjects	
present	7
absent	11

from that in the other groups. Hence in the ANCOVA the gender and diagnostic groups were used as factors and age was a covariate. Gender and age effects were also 'partialled out' in estimations of correlation coefficients. All the patients with MDD had unipolar depression and were treated by the clinical team with tricyclic antidepressants and/or electroconvulsive therapy (ECT) purely on clinical grounds. The SPECT was performed in the depressed patients before any ECT they received as part of their treatment.

The results of the visual reports on the scans (Table III) showed that more MDD and AD patients showed impaired regional cerebral perfusion than control subjects. The relevance of SPECT in studying the cerebral changes in depression is illustrated by one patient with MDD, who showed no abnormality on CT scan (Fig. 1) but markedly impaired perfusion on SPECT (Plate V).

TABLE III
Number of subjects showing impaired regional perfusion on qualitative assessment of SPECT scans

Regions involved	*Healthy control subjects* (n = *12*)	*Depressed patients* (n = *18*)	*Alzheimer's disease patients* (n = *14*)
Left frontal	1	6	12**
Left temporal	3	8	8
Left parietal	1	8	10*
Left occipital	0	5	6
Right frontal	1	7	12**
Right temporal	2	9	8
Right parietal	1	8	8
Right occipital	0	5	4
At least two cerebral regions	2	8	13**

$^{*}P<0.025$, $^{**}P<0.005$, χ^2 test.

The comparison of the uptake ratios across the groups is given in Table IV. The mean ratios in all the cerebral regions of the depressed patients were intermediate between those of the AD patients and the control subjects. The difference is statistically significant for the total and almost reaches the levels of significance in the left temporal and right parietal regions.

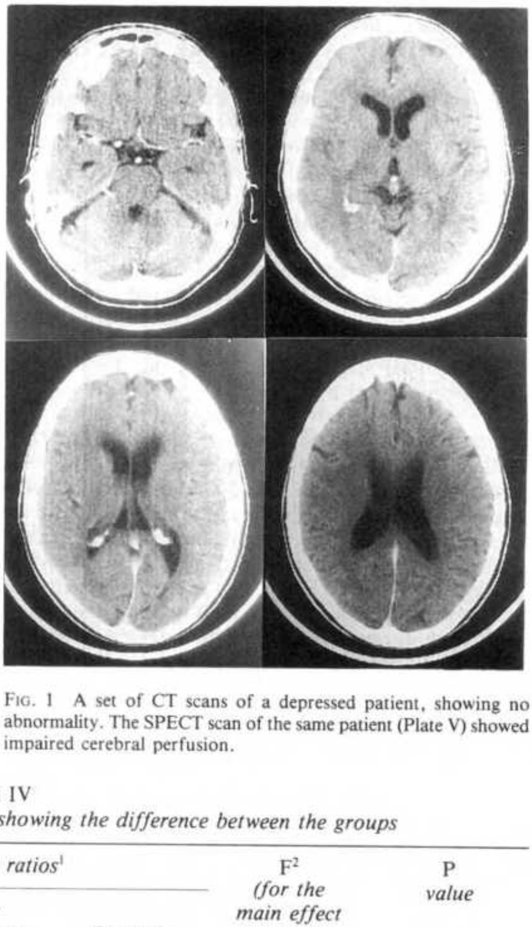

FIG. 1 A set of CT scans of a depressed patient, showing no abnormality. The SPECT scan of the same patient (Plate V) showed impaired cerebral perfusion.

TABLE IV
Analysis of covariance of the uptake ratios[1] showing the difference between the groups

Cerebral region	*Mean uptake ratios*[1]			F[2] *(for the main effect of group)*	P *value*
	Alzheimer patients (n = *14*)	*Major depressives* (n = *18*)	*Controls* (n = *12*)		
Left occipital	0.94	0.97	1.00	1.97	0.15
Right occipital	0.93	0.98	1.00	3.01	0.06
Left temporal	0.87	0.92	0.95	3.20	0.05
Right temporal	0.87	0.91	0.94	2.29	0.11
Left parietal	0.83	0.87	0.90	1.87	0.17
Right parietal	0.81	0.86	0.89	3.23	0.05
Left frontal	0.76	0.78	0.85	2.97	0.06
Right frontal	0.73	0.76	0.81	2.65	0.08
Total	0.84	0.88	0.92	3.46	0.04

1. Uptake by the cerebral regions of interest:uptake by the cerebellum.
2. All *F* values are with 2 and 41 degrees of freedom. The *F* values for the main effect of gender, the interaction of the main effects and for the covariate were not significant.

The partial correlation between the Newcastle score for 'endogenicity' in the depressed patients and the regional uptake ratio, controlling for age and gender, was found to be negative in all regions, but reached levels of significance in right and left occipital areas ($r=-0.64$ and -0.56, $P=0.008$ and 0.024, respectively). The partial correlation between the HRSD scores of depressed patients and the regional uptake ratios was not significant in any of the cerebral regions, although it was negative for most areas, the highest correlation being in the right occipital region ($r=-0.31$, $P=0.24$).

Analyses of covariance were also carried out to examine the difference in the rCBF parameter between those with and without a past history of depression, but no difference was found. Analysis of covariance was also carried out across the three groups of subjects to examine any differences in the left–right asymmetry of uptake ratios in the patients compared with the controls. The ratio of the differences between left and right regional uptake ratio and the sum of the left and right uptake ratio was used as an index of regional asymmetry in perfusion. Using age as a covariate, ANCOVA was carried out with group and gender as the main factors, because the lateral asymmetry in regional perfusion in females was more biased in favour of the left side, compared with the male subjects. No group difference in the lateral asymmetry in perfusion was found, but in the temporal area the main effect of gender was significant.

Discussion

The present study demonstrates regional cerebral perfusion impairments in elderly depressed patients, which is in keeping with the findings of a number of recent studies (Devous *et al*, 1984; Sackeim *et al*, 1990). Sackeim *et al* (1990) showed that the reduction in cerebral perfusion in major depression was similar in magnitude to that seen in AD (Prohovnik *et al*, 1988). Although the difference in the activity ratios between the groups in the present study failed to reach statistical significance, the trend is very strong. This could partly be due to the small sample size and the wide variation in the severity of dementia in AD patients. The method used in the study for assessment of cerebral perfusion is indirect and does not yield absolute values. However, this index of cerebral perfusion has been shown to be a valid measure, as the perfusion indices correspond to discrete neuropsychological deficits in patients with AD (Burns *et al*, 1989). Cerebral perfusion and glucose metabolism are tightly coupled on a local basis (Baron *et al*, 1982). While decoupling may occur in some neurological diseases there is no reason to suspect that this occurs in major depression.

The cause of the rCBF deficits in major depression is unknown. It is unlikely to have a primarily vascular origin, as the distribution of impaired perfusion shown by Sackeim *et al* (1990) does not conform to any topographical distribution of the major blood vessels in the brain. In our study, we specifically excluded individuals with significant vascular pathology. Hence this question of any possible relationship between vascular pathology and the impaired perfusion in the elderly depressed remains unanswered.

There are several lines of evidence suggesting cerebral changes in depression, particularly in the elderly. Apart from impaired cerebral perfusion, there are neurochemical and neuroanatomical changes in depressed patients, which are similar to those in patients with degenerative dementia (Seiver & Davis, 1985; Alexopoulous *et al*, 1988). Several clinical studies point towards an interface between depression and dementia in the elderly. Although earlier studies minimised the cognitive changes observed in depressive illness and treated them as instances of pseudodementia, many recent studies have confirmed that depression is not uncommon among patients with primary degenerative dementia, and many elderly depressed patients progress to established dementia (Reifler *et al*, 1982; Reding *et al*, 1985; Lazarus *et al*, 1987).

Pearlson *et al* (1989) reported the CT changes in two groups of elderly depressed subjects, one with cognitive decline severe enough to merit a diagnosis of dementia, and the other cognitively normal. Their findings suggest that these two groups differ in the extent of neuroanatomical abnormalities as measured by CT attenuation and ventricle:brain ratios (VBR). The CT values of the whole depressed group lay between those of AD patients and normal controls, but the CT values of depressed patients with dementia syndrome clustered near those of AD patients.

It is not yet clear whether the cerebral changes accompanying depressive illness are state dependent. There is some evidence that the cognitive impairment and the impairments in rCBF are not always completely reversible. Ventricular enlargement on the CT scan have been reported in young patients with affective disorders (Pearlson *et al*, 1984) and it is possible that the neuroanatomical changes shown on CT scan in depression are the result of irreversible structural abnormalities.

The prognostic implications of the cerebral changes in depression remain unclear. The similarities between the elderly depressed and AD patients suggest that the CT changes as well as the rCBF impairments of depression could well be precursors of a progressive dementing illness (Kral, 1983; Reding *et al*, 1985), but the study by Pearlson *et al* (1989) showed that on retesting after two years, all but one of the depressed patients presenting with a dementia syndrome when ill were free from cognitive decline. Moreover, reports of high rates of dementia on follow-up of depressed patients (Reding *et al*, 1985) were possibly biased in the sample selection so as to include many with neurological disorder, and the conclusions could not be extended to depressed patients in general. Hence the cerebral changes observed in depression may not directly point to a progression to degenerative dementia, at least in the short term. The prognostic implications of these changes can only be established by studies involving repeat measures and long-term follow-up.

This study also aimed to examine any possible relationship between severity or the nature of depression and the impairment in cerebral perfusion. No correlation was found between scores on HDRS and the indices of cerebral perfusion. The small sample size precludes a firm conclusion on the absence of correlation, but the study by Sackeim *et al* (1990) also failed to show any significant correlation. This study suggests that patients with endogenous depression are more likely to have impaired rCBF.

The prognostic implications of rCBF impairment in the elderly depressed are important not only for a better understanding of the pathophysiological basis of depression, but also in delineating subgroups of depressed patients. The patients of the present study are being followed up with a view to examining this issue.

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Positron Emission Tomography in the Study of Brain Metabolism in Psychiatric and Neuropsychiatric Disorders

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Positron emission tomography (PET) differs fundamentally from computerised tomography (CT) and magnetic resonance imaging (MRI) in that it is a method for measuring function as opposed to structure. It is the most powerful tool available for the measurement of *in-vivo* brain function. This review describes the basic principles of the technique and its application to the study of brain metabolism in neurological and psychiatric disorder. The development of resting-state metabolic studies by the application of specific activation paradigms, a major current focus of the technique, is discussed.

Principles

The feasibility of PET is dependent upon the availability of compounds that can be labelled with positron-emitting nuclides. The signal measured in PET is derived from the decay of those radioactive substances, which are introduced into the body either by intravenous injection or by inhalation. The most useful and most commonly used nuclides are oxygen-15, carbon-11 and fluorine-18 with half-lives of 2.1, 20.4 and 110 minutes respectively. These are essentially ideal in that their substitution into molecules of biological interest does not alter the behaviour of the compound in the body from that of the stable parent compound. Fluorine-18 usually substitutes for a hydrogen atom in a molecule that will normally contain no stable fluorine; even such relatively minor substitutions may subtly alter biological properties. The short half-lives of the commonly used tracers makes an on-site cyclotron a prerequisite for a PET centre. Recent developments of mini-cyclotrons and automated 'black-box' production of tracers may diminish the capital outlay necessary to perform PET at the expense of constraining the range of possible studies. The major advantage of using tracers with a short half-life is that this ensures a low radiation dose to the subject, enabling repeat studies, if necessary even within the same scanning session. This has particular relevance to the development of activation paradigms using dynamic estimations of blood flow.

Positrons, which are positively charged electrons, when emitted from decaying nuclei, travel a short distance (1–3 mm) in tissue until they interact with an electron, resulting in an anhihilation reaction. This reaction releases two gamma rays of equal energy (511 keV) which travel in exactly opposite directions. A detector system of high sensitivity placed circumferentially around the head can map the distribution of the positron-emitting nuclide. These detectors are electronically linked by coincidence circuits so that only the simultaneous arrival of gamma rays at two opposite detectors is registered as an 'event'. Using standard computerised reconstruction techniques, in conjunction with coincidence detection, it is then possible to map the spatial and temporal distribution of the positron-emitting nuclide (Ter-Pogossian & Phelps, 1975; Huang *et al*, 1979; Hoffman *et al*, 1979). Loss of signal due to attenuation by brain tissue can be corrected by performing a transmission scan, in which the subject is exposed to an external ring source of radioactivity located within the scanner, before the emission study. With the latest detector systems it is possible to obtain up to 31 contiguous slices of data from the 10.8 cm of the head scanned. In-plane resolution of the order of 5 mm has been obtained with scanners that are at the present limits of technological sophistication. Sensitivity of detection is exquisite, such that picomolar concentrations of radiolabelled substances can be measured. By comparison, magnetic resonance (MR) spectroscopy has a sensitivity in the tens to hundreds of millimolar range. With suitable calibration, the tissue tracer distribution can be recorded in absolute physical units of radioactivity (Ci/ml). The PET camera therefore is a measuring instrument in addition to an imaging device.

PET methods of measurement of brain metabolism

The data acquired in a PET study need to be understood and expressed in terms of some physiological, biochemical or pharmacological process. This is achieved using a model, which in its simplest form is a mathematical description of the biological process being measured in terms of the temporal and spatial fate of the tracer, such that the parameter of interest can be derived. Mathematical models are generally used to incorporate known information about a process so as to provide a framework or representation that allows the interpretation of measurements. The simplest methods are those used to measure tissue metabolism. PET measurements of metabolism depend on the fact that in the adult brain functional activity is almost entirely dependent on oxidative metabolism requiring oxygen and glucose as substrates (Siesjo, 1978). Rates of metabolism can be determined by measuring the rate of utilisation of a substrate, as in the oxygen technique (Frackowiak *et al*, 1980), or the accumulation of a product, as in the deoxyglucose technique (Phelps *et al*, 1979; Reivich *et al*, 1979). The detail of these methods is beyond the scope of this review and the reader should refer to previous comprehensive reviews (Phelps *et al*, 1986; Baron *et al*, 1989).

Clinical application of PET

A PET scan can typically last between 45 minutes for a resting metabolic or flow scan and two or more hours for a study using a pharmacological tracer. Preparation for the scan involves fabrication of a head holder to ensure immobility during the scan, and insertion of a radial artery catheter. The latter is required to enable sampling of arterial blood during the scan, in order to measure the amount of tracer in the blood and accurately define the arterial input function to the brain. Maintenance of head position during the scan is of crucial importance in increasing the signal-to-noise ratio.

The use of a head holder inhibits gross movement within the scanner but finer movements are more difficult to control. The inherent intersubject variability in brain size and shape is a further important confounding variable in identification of the site of origin of a functional signal. These problems have been addressed in a number of ways. A structural (MR or CT) scan may be taken with an external frame of reference to allow cross-modal (structure–PET) matching. If this is not the case, then structures in the PET images have to be identified by inspection. This is justifiable in some PET images such as ^{18}F-DOPA images of the basal ganglia, but it is not an ideal approach to metabolic images. The method used at the MRC Cyclotron Unit at the Hammersmith Hospital involves the matching of each individual PET scan to a standard PET template in a least-squares sense. This template has a predetermined relationship (Friston *et al*, 1989) to a standard stereotactic space (Fox *et al*, 1988; Talairach & Tournaux, 1988). This avoids the need for a structural scan while maximizing the probability that a signal from the same place in two images relates to the same part of the brain. To illustrate the problem, and this solution, Plate VI shows two schizophrenic brains before and after elastic transformation into a standard reference space.

The confinements of the technique may lead to bias in patient selection, particularly where cognitive or perceptual disturbance leads to agitation, perplexity and behavioural overactivity. This has particular relevance for studies of dementing or psychiatric patients and is discussed in more detail below.

Data acquisition

The methods sections of many papers detail a number of technical specifications which relate to the nature of the images acquired. Many of these are of little importance, particularly with reference to established protocols such as for the estimation of regional cerebral blood flow (rCBF) and regional cerebral metabolic rate of glucose. One specification which should be noted is the number of planes acquired. This can vary from 3 to 31 and for values of less than 15 there is likely to be 'dead space' – interplane cerebral tissue not seen by the camera. In studies with small plane numbers, or those reporting a single plane at a time, the signal in a region of interest (ROI) (e.g. for the caudate) will reflect both the proportion of the total volume of the caudate represented within the plane and its activity. This extra source of error will predispose to type 2 errors.

The full width at half maximum (FWHM) is a measure of the camera's resolving power and is typically 8 mm. Studies on machines with a larger FWHM are as 'good' as 'high-resolution' PET. This is because all data analysis begins by 'smoothing' the images, either directly or, by definition, when using ROIs.

Changes in metabolism with ageing

Studies of normal ageing using PET have concentrated on defining the normal regional changes in cerebral metabolism (of oxygen and glucose) and haemodynamics. Measurements of glucose metabolic rate (Kuhl *et al*, 1982; Duara *et al*, 1983) have yielded less consistent results than measurements of oxygen metabolism in relation to blood flow, performed extensively using the steady-state oxygen inhalation technique (Frackowiak *et al*, 1980). The salient points of these studies are that there is an age-related decline in blood flow in grey matter but not white matter and that this is not paralleled by a decline in the metabolic rate of oxygen. There is a trend towards increased oxygen extraction (OER) reflecting the maintenance of metabolism in the face of declining flow.

Dementia

Global changes

In contrast to the normal ageing process, patients with Alzheimer's disease (AD) have a progressive decline in both CBF and metabolic rate of oxygen in grey matter which correlates with the severity of cognitive impairment. This metabolic decline is also seen in white matter. In terms of global changes of metabolism, decreases of up to 50% of normal control values have been reported. The coupled relationship between CBF and metabolic rate of oxygen holds for both hemispheric and regional analysis, with emphasis on posterior temporal and parietal regions (Frackowiak *et al*, 1981). As yet, it remains uncertain whether the changes demonstrated reflect diminished neuronal numbers or diminished metabolism in numerically normal neurons. PET studies using fluorodeoxyglucose have also shown significant decreases in the metabolic rate of glucose in the same temporoparietal regions (Friedland *et al*, 1983).

For any condition studied, the interpretation of local changes in activity will be confounded by the global change. In most conditions what is of interest is the true regional change and its relationship to discrete symptoms, signs, or activation by specific neuropsychological or pharmacological paradigms. In order to delineate this regional effect, the global activity must be normalised. Methods of normalisation range from simple division by a global mean to *post-hoc* statistical adjustments (Friston *et al*, 1990). Whatever the method used it is important to bear in mind that statements about regional differences can only be relative. For example, hypofrontality may well be hyperoccipitality. If data have been normalised there is no way of distinguishing between the two. If no normalisation has been applied then regional differences will be confounded with global differences.

Morphological changes in dementia

Structural imaging has demonstrated gross morphological brain changes in AD, particularly cortical atrophy. These latter changes could introduce problems of quantification in PET, in that the presence of non-neural elements within the volume might influence functional measurements. As yet there are no entirely satisfactory methods for correcting for these partial-volume effects, although systematic correction of the PET image on a pixel-by-pixel basis with reference to high-quality MR imaging has been described (Videen *et al*, 1988). It can be assumed therefore that calculated values for energy metabolism reported in the literature are an overestimation of the true decrease in metabolism.

Focal changes

Oxygen and glucose methods have found similar patterns of regional pathophysiology in AD. Deficits in metabolism have an emphasis initially in the parietal and adjoining parts of the posterior temporal cortex and anterior occipital cortex. Progression of the dementia is associated with decreased frontal metabolism, but with relatively little further change in the temporoparietal regions. Characteristically the primary motor and sensory cortex and striatum are relatively spared (Frackowiak *et al*, 1981). Focal abnormalities have been correlated with clinically determined impairments (Chase *et al*, 1984*a*; Foster *et al*, 1984, 1986). In particular, aphasia, apraxia and visuospatial function have been correlated with changes in metabolism in the appropriate hemisphere. The levels of clinical effects correlating with decreased metabolism in AD have been reviewed by Huxley & Rapoport (1986). Firstly, reductions in whole-brain metabolism are related to overall severity of dementia. Secondly, regional hypometabolism in the association cortices exceeds that in primary sensorimotor cortex, corresponding to marked impairment of higher cognitive function. Thirdly, greater metabolic asymmetry is accompanied by disproportionate neuropsychological deficits in either language or visuospatial functions, depending on whether the hypometabolism is in the dominant or non-dominant hemisphere, respectively.

A group of conditions increasingly recognised clinically are the so-called focal degenerations which present initially with highly selective neuropsychological impairments, most commonly aphasia. Both clinical and neuropathological findings suggest that these are distinct conditions from Alzheimer's disease (Mesulam, 1982). Gross structural brain changes are not usually apparent in the early phase of these disorders, though PET can reveal alterations in metabolism before the development of structural change (Tyrrell *et al*, 1990). The pattern of altered metabolism is frequently highly focal and distinct from that seen in early AD. The ability to perform serial studies on these patients should help to clarify the nosological status of these conditions and the degree to which they are truly focal or generalised degenerations with an early focal emphasis.

Multi-infarct dementia and cerebrovascular disease

Pathological studies show that the substrate for vascular dementia is the cumulative effect of multiple ischaemic infarctions, usually with strategic placement and exceeding a threshold volume (Tomlinson *et al*, 1970). The pathophysiological sequence in the acute events is a fall in perfusion pressure and flow to below 50% of normal. At this stage oxygen extraction (OER) is maximal and the ischaemic threshold is crossed. Depending on the depth and duration of ischaemia, cell death and/or frank infarction will occur. This phase is characterised by a low oxygen metabolic rate with high OER which rapidly changes to low metabolic rate and low OER when neuronal damage occurs (Wise *et al*, 1983). At some time following a stroke, tissue reparative processes usually lead to recoupling of CBF and oxygen metabolic rate and normalisation of OER.

Multi-infarct dementia (MID) produces global reductions in cerebral metabolism but in addition there are focal and asymmetric areas of hypometabolism, not confined to any particular brain region. Various studies have demonstrated multiple lesions in cortex, deep nuclei, subcortical white matter and cerebellum (Frackowiak *et al*, 1981; Kuhl *et al*, 1985*a*,*b*). Typically, more widespread brain involvement is detected by PET than by CT, consistent with the finding that single lesions may have extensive and distant metabolic sequelae. Characteristically, increasing severity of dementia correlates with global hypometabolism and increasing involvement of the frontal cortex.

More striking examples of alterations in metabolism are seen in patients who have experienced isolated lacunar infarcts, detected by structural imaging, affecting cortical or subcortical grey matter. These discrete anatomical lesions frequently produce cerebral metabolic effects at sites distal to the ischaemic lesion, which are not detected by conventional imaging techniques. An example of this phenomenon is the contralateral cerebellar metabolic depression or cerebellar diaschisis, seen following cortical cerebral vascular lesions (Baron *et al*, 1981). Similar effects are seen with lacunar infarcts of deep grey matter. Baron *et al* (1986) demonstrated significant ipsilateral cortical hypometabolism affecting the entire cortical mantle following thalamic infarcts. A number of single case reports of isolated subcortical lesions, mainly thalamic, have demonstrated similar patterns of distal metabolic depression. These findings raise a number of important points, particularly relating to extrapolations from clinicopathological relationships, and are discussed further below.

Pick's disease and 'frontal' dementias

Pick's disease has a metabolic profile distinct from that of AD and MID, with marked bilateral frontal hypometabolism (Franck *et al*, 1986). 'Dementia of frontal lobe type', distinct from Pick's, has recently been described (Gustafson *et al*, 1985; Neary *et al*, 1988). Measurements from single-photon emission computerised tomography (SPECT) in these patients indicate reduced metabolism in the frontal lobes. It is of interest that both AD and MID show increasing 'frontality' in clinical terms and hypometabolism, as assessed by PET, with disease progression. Whether or not hypofrontality is an entirely specific finding, determined by local neuropathological changes, is open to question. It is possible that frontal areas are 'recruited' according to distribution of neurotransmitter systems that are primarily affected by degenerative change in crucial distant (subcortical) regions of origin. The finding of hypofrontality in functional psychiatric disorders and the effect of deep lesions in animal models lends validity to the non-specific notion of hypofrontality. For example, Kiyosawa *et al* (1987) showed significant metabolic depression in the ipsilateral fronto-temporal cerebral cortex following electrocoagulation of the left nucleus basalis in five baboons. In addition, D'Antona *et al* (1985) found that eight patients with a presumed diagnosis of progressive supranuclear palsy had a highly significant decrease in glucose metabolism in the pre-frontal regions. These findings also question the validity of the clinical distinction between the cortical and subcortical dementias.

PET in psychiatric disorders

In psychiatric disorders, structural imaging studies have isolated subgroups of patients with non-specific brain changes, usually atrophic. However, the majority of patients with major psychiatric illness (schizophrenia or manic–depressive psychosis) have brains that appear normal with present structural imaging. Abnormalities in these disorders are likely to be functional, with symptoms generated by, or related to, the activity and integration of neural networks.

Patient selection is a major problem in psychiatric studies and bias may conceivably be introduced at at least two stages. Firstly, diagnostic criteria tend to emphasise 'positive' symptoms such as delusions and hallucinations, with the result that subsyndromes with less florid symptoms may be under-represented in studies. This is a particular problem in studies of schizophrenic patients. Secondly, the confinements that scanning imposes (head mould, administration of radiopharmaceutical by inhalation or injection, arterial cannulation) are of critical importance in psychiatric patients who may be sensitive to external stresses and subject to abnormal beliefs and experiences. Therefore selection may occur at the scanning stage, with more disturbed patients unable to tolerate one or more of the procedures involved. It is with these problems in mind that increasing attempts are made to identify nosologically pure subgroups of patients. This may involve studying groups with identified biological markers such as neuroendocrine indices, genetic markers from molecular biology techniques or well circumscribed cognitive/neuropsychological deficits, in addition to initial diagnosis according to standardised diagnostic categories such as those from DSM–III (American Psychiatric Association, 1980) or Research Diagnostic Criteria (Spitzer *et al*, 1977). Once identified, specific activation paradigms, in terms of neuropsychological or neuropharmacological challenge, may be applied to these groups, with the anticipation that sensitivity and specificity of the functional scanning technique will be enhanced with respect to resting conditions.

In order to fulfil the potential of advances made in activation protocols, analysis of PET images needs to be standardised, with particular emphasis placed on moving away from the traditional ROI analysis. A pixel-by-pixel approach will enable both hypothesis-led and more speculative analysis to be made without the constraints of ROIs whose boundaries bear little relationship to functional neuroanatomy.

The following sections review findings from previous PET studies of psychiatric disorders, with emphasis placed on study design and data analysis.

Schizophrenia

Schizophrenia has been studied more than any other psychiatric disorder using PET but there have been very few consistent findings in the ten years PET has been used in this field. As with many other investigative approaches, this is probably due to the variability and multiple concomitants of schizophrenia. To complicate matters PET has evolved considerably in technical terms over the years and earlier results are difficult to compare with more contemporary findings.

The majority of studies have tried to find a regional cerebral dysfunction associated with schizophrenia. To this end small numbers of schizophrenic subjects have been scanned cross-sectionally and compared with normals. This class of study has, on the whole, lent support to the notion that schizophrenics evidence 'hypofrontality'. There are however many studies in which this is not the case. A smaller number of studies go further than this and relate regional dysfunction to a specific pharmacological or neuropsychological function. This has involved correlating indices of regional cerebral activity with dose of drug taken, psychological test performance, clinical ratings or, more recently using 'activation' designs.

Hypofrontality

The pioneering work of Ingvar (1974) and contemporaries, using xenon inhalation techniques to estimate blood flow, provided the first evidence for hypofrontality. Contemporary replications should be viewed in a more critical light. The concept of hypofrontality was based on empirical findings and constrained by the available techniques, which had very limited spatial resolution. Neuroanatomically or physiologically, the idea that the entire frontal lobes change metabolically as a single unit while the non-frontal regions remain a stable reference is not tenable. The pre-frontal cortices are diverse functionally and architectonically. They include both granular and agranular cortex with markedly different ontology, neural connections and functions. Medial cortices include SMA, the anterior cingulate, contigious paralimbic cortex and granular cortex. The lateral cortices include Brodmann's areas 46, 9 and 8 as well as pre-motor areas and area 44. The range of functions includes eye movements (frontal eye fields), and motoric speech (Broca's area). Psychiatric sequelae of lesions to the medial and lateral cortices are different and have formed the basis of classifications of frontal-lobe syndromes (Blumer & Benson, 1975). Work in our own unit, done in collaboration with Dr C. Frith, highlights this functional dissociation within the pre-frontal cortices. Plate VII shows images of the significance of cerebral activation associated with intrinsically generating words (verbal fluency) and intrinsically generating random motor responses. These images are pictures of significant cerebral blood-flow change induced by activation, superimposed on the Talairach proportional grid (Talairach & Tournaux, 1988) which describes the most commonly used anatomical reference space used in PET.

DeLisi *et al* (1985*a*) studied patients with chronic schizophrenia and matched controls. The patients met strict DSM–III criteria for schizophrenia and were free of medication for at least two weeks before the study. Patients had significantly lower anterior: posterior ratios (8 of the patients had ratios less than 1). Cerebral atrophy determined by CT was not associated with this aberrant metabolic pattern. Gur *et al* (1987*a*,*b*) described abnormalities of the subcortico-cortical metabolic gradient in schizophrenic patients who were free of medication for at least a week. The duration of illness varied from 3 to 17 years. No evidence for hypofrontality was found. Finally, Szechtman *et al* (1988), in a controlled study, examined whether duration of neuroleptic treatment influenced the regional distribution of metabolism in patients meeting Research Diagnostic Criteria (RDC) for schizophrenia. The patient group was dichotomised according to treatment duration. Both groups had a greater anterior: posterior (hyperfrontality) ratio than controls, though this was less evident in the group with the longest exposure to neuroleptics.

Explanations for these apparently inconsistent results include the confounding effects of treatment and illness duration, differences in scanning procedure, especially correction for attenuation, and in image analysis. An important consideration is the relative preponderance of positive and negative symptoms in the groups studied. In this context Liddle (1987) has described three subsyndromes of schizophrenia which include a syndrome of 'psychomotor poverty' characterised by negative symptoms (flat affect and poverty of speech and spontaneous movement). Based on a comparison of signs and symptoms in focal brain lesions it is suggested that this syndrome is associated with impaired pre-frontal cortical function. The prediction that hypofrontality is associated with negative symptoms has received some support from PET studies. Delisi *et al* (1985*b*) reported that the only significant correlations between relative hypofrontality and symptom ratings were for emotional withdrawal, disorientation, distractability and helplessness/hopelessness. Kishimoto *et al* (1987) discriminated between three distinct types of metabolic pattern in chronic schizophrenic patients. Hypofrontal patients tended to show flat, blunted affect, and a hypoparietal group delusions and hallucinations.

Specific associations between symptoms and regional dysfunction are revealed by correlational analyses with the schizophrenic group. It is possible that comparing schizophrenics with schizophrenics, and avoiding uncontrollable confounding variables, will prove a fruitful strategy. This approach is best exemplified by the demonstration of three distinctive rCBF profiles in a group of 30 chronic schizophrenics split orthogonally, three ways, according to Liddle's subsyndromes (Liddle *et al*, 1990).

The possible relationships between negative symptoms, hypofrontality and putative abnormalities of the mesocortical dopaminergic system have been addressed from a number of perspectives. Animal studies using autoradiography have shown increased frontal and anterior cingulate metabolic response to the dopaminergic agonist apomorphine (McCulloch *et al*, 1982). Corresponding dopaminergic challenge in humans has yet to be established, although initial studies have been reported. Wolkin *et al* (1987) report decreased frontal, temporal and striatal glucose metabolism in schizophrenics and controls following *d*-amphetamine (0.5 mg/kg p.o.). Geraud *et al* (1987) report a reversible haemodynamic hypofrontality in young schizophrenics. Hypofrontality was seen in chronic patients whose disease had evolved over more than two years and this pattern disappeared during exacerbation of the symptoms. In a subgroup who had not been treated for several weeks, a weak dose of a dopaminergic agonist restored near-normal frontality. The authors conclude "this [dopamine hypersensitivity] may reflect either the role of neuroleptic washout or a primitive dopaminergic depletion as proposed by some authors in the chronic form of schizophrenia".

Therefore, hypofrontality is not always found and may critically depend on the type of schizophrenia being studied.

Cognitive/sensorimotor activation

Making PET a behaviourally or pharmacologically specific technique is the object of activation paradigms. Behavioural specificity can be achieved by using PET in conjunction with cognitive or sensorimotor activation. Regional deficits measured with PET can be seen as a common mediator of clinical and neuropsychological symptoms. The resting levels of regional blood flow or metabolic rate in psychiatric patients may not be markedly different from those of normals (Sheppard *et al*, 1983); however, the increase in cerebral activity brought about by a cognitive task may differ considerably. This increased sensitivity may reveal correlations between clinical ratings and cerebral activity that were previously hidden. Using ^{11}C deoxyglucose as a PET tracer, Volkow *et al* (1987) studied patients with chronic schizophrenia using a smooth-pursuit eye-tracking activation task. This task was chosen because performance is impaired in some schizophrenics and impairment is associated with dysfunction of the frontal cortex. Significant differences between conditions were observed solely in the patients with positive symptoms. The authors note that there were more significant correlations between metabolic rate and clinical items during the task condition. In particular negative correlations were found between left frontal metabolic rate and some ratings on the Brief Psychiatric Rating Scale. This study illustrates how activation studies may increase not only the specificity but also the sensitivity of PET.

Cohen *et al* (1987) studied cerebral function during an auditory discrimination task designed to emphasise sustained attention. A direct relationship was found between metabolic rate in the pre-frontal cortex and accuracy of performance. In schizophrenics lower pre-frontal flow was unrelated to task performance.

Warkentin *et al* (1989), using a xenon inhalation measurement of rCBF, used a verbal-fluency task as a cognitive challenge. The most marked effect of the activation in normals was seen in the left pre-frontal area, but in the schizophrenic group this increase was attenuated. The authors concluded "the controversy regarding frontal lobe dysfunction in schizophrenia is related to whether these areas are functionally challenged or not".

Specificity is implicit in the design of the activation. If impaired augmentation of regional cerebral activity is associated with a specific cognitive task, then the deficit has both a neuroanatomical and a functional specificity. Linking of cortical and neuropsychological dysfunction is illustrated by the work of Weinberger *et al* (1988). Using xenon-133 inhalation to measure rCBF, this group has shown that chronic schizophrenics fail to activate the dorsolateral pre-frontal cortex (DL-PFC) during the Wisconsin Card Sort Test (WCS). The baseline in these studies was a simple number-matching task. They extended the specificity of this "behaviour-specific hypofunction" by demonstrating significant correlations between DL-PFC rCBF during the WCS and cerebrospinal fluid levels of dopamine and serotonin metabolites.

Pharmacological activation

Short-term longitudinal studies in conjunction with pharmacological challenge permit the changes in cerebral activity following manipulations of specific neurotransmitter systems to be identified. Cleghorn *et al* (1990) have studied the effect of apomorphine on neuroleptic-naive first-episode schizophrenics and controls. They found a bilateral increase in the 'caudate' frontal area in the control group. At low doses McCulloch *et al* (1982) demonstrated increases in frontal gluclose metabolism in layers IV and VI in their autoradiographic studies in animals. A simple interpretation is a pre-synaptic hyperpolarising effect of apormorphine on ascending dopaminergic projections, resulting in an indirect disinhibition of cortical activity. In Cleghorn's study the schizophrenics failed to evidence increases in frontal metabolism, further implicating frontal dopaminergic projections in schizophrenia.

Future directions

There have been no long-term studies of schizophrenia. Activation studies involve repeated scanning in different brain states and represent short-term longitudinal designs which hold great promise. These studies require a method of rapid CBF estimation such as that described by Raichle *et al* (1983) and Lammertsma *et al* (1989). Other techniques suggest that combined activation studies are going to be an important area. Daniel *et al* (1990) have used SPECT to measure changes in rCBF in chronic schizophrenics while performing the WCS and a simple control task. These changes were measured in the presence and absence of dextroamphetamine using a double-blind, placebo-controlled, cross-over design. Amphetamine produced a task-independent reduction in global CBF. With amphetamine there was a significant activation of the left DL-PFC, while with placebo there was no such activation. Furthermore, WCS performance improved considerably in the drug condition. The authors conclude "these findings are consistent with animal models in which mesocortical dopamine activity modulates and enhances the signal to noise ratio of PFC activity". It is interesting that Pycock *et al* (1980) note "Lesions of either midbrain cell bodies in the VTA or of frontal cortical areas directly, with subsequent loss of DA terminals in the prefrontal cortex, induce hyperactivity in rats and enhanced behavioural responses to amphetamine".

Affective disorders

The aetiology of the affective disorders is still unknown. The efficacy of antidepressant medication implicates abnormal neural transmission in monoaminergic pathways in neural networks in critical brain regions involved with mood regulation. However, the specific anatomical regions involved have yet to be delineated. This failure has frequently been ascribed to the lack of direct measures of brain function *in vivo*.

In contrast to schizophrenia there have been relatively few studies of patients with affective disorders. The earliest study compared regional cerebral metabolic rates of glucose in schizophrenia, affective disorder and control subjects using a somatosensory paradigm (1 Hz electric shocks to the right forearm) to attempt to control for ambient state across subjects (Buchsbaum *et al*, 1984). The affective patients showed a reduced 'anteroposterior (AP) gradient' in glucose metabolism compared with normal subjects, a finding that was repeated in the schizophrenic group. There were no differences between the affective and schizophrenic groups, which was explained on the one hand by small sample size (16 schizophrenics and 11 affectively disordered), diagnostic heterogeneity among both groups, and range of severity of the mood disturbance, and on the other hand by suggesting that the reduced AP gradient could be a generalised feature of both illnesses – a core biological feature of the psychoses. The order of magnitude of these changes was similar to that seen in multi-infarct dementia (Kuhl *et al*, 1985*b*).

Region-of-interest analysis was used in the above study and this has been the approach adopted to date in most PET studies. The problem with ROI analysis is simply that any results are in terms of the ROIs chosen. ROIs have little validity in terms of functional anatomy, and none in terms of cytoarchitectonics. Attempts to avoid subjective bias in selection of ROIs include use of computer algorithms to identify brain areas. Reiman *et al* (1984, 1986) used a stereotactic method of anatomical localisation in which co-ordinates from a stereotactic atlas and measurements from a lateral skull radiograph are entered into a computer program that generates the co-ordinates of the desired regions in the PET image. Data from these regions are recorded without visual inspection of the image and are thus free from observer bias. However, even if ROIs were partially validated in terms of gyral anatomy they will still fail to be proper topographic descriptions of distributed functional systems. Therefore a major development in analysis of PET data is the move towards pixel-by-pixel analysis. To this end, Fox *et al* (1988) have developed an automated data-analysis technique which identifies significant changes in rCBF in volumes of pixels (voxels). Pixel-by-pixel analysis is more valid primarily because the spatial extent and location of any change is constrained solely by the data. This is even more important in the study of neurotransmitter systems which are not subject to 'parcellation' or sulcal delimitation.

With these limitations in data analysis in mind, only one study of affective disorders to date has failed to report 'hypofrontality' (Kling *et al*, 1986). In this study only six "chronically depressed" patients were studied, with diagnostic criteria unspecified for one case. Further heterogeneity in this group included the presence of increased ventricular brain ratio (VBR) in four of the six patients.

A detailed series of studies has been reported by members of the group from the University of California, Los Angeles (UCLA) (Phelps *et al*, 1984; Baxter *et al*, 1985; Schwartz *et al*, 1987). In the earliest study, 14 patients with unipolar depression had scans, six being repeated after a pre-dose of 15 mg methylphenidate and four having a third scan when euthymic. Seven bipolar manic and five bipolar depressed patients were also studied, with three subjects rescanned in a euthymic state. Seven age-matched controls were scanned with and without methylphenidate. Overall, patients with bipolar depression had a highly significant decrease in hemispheric metabolic rate for glucose when compared with all other groups, including unipolar depressives. A subgroup of the unipolar depressives had asymmetries limited to frontal temporal cortex, most prominent in the postero-inferior portion of the frontal cortex and in the anterior superior portion of the temporal cortex. Within this group, the subgroup who showed asymmetric hypometabolism (left less than right) had a positive clinical response to methylphenidate which correlated with a normalisation of the baseline metabolic asymmetries.

In the second study of the series, cerebral glucose metabolic rate was examined in 11 patients with unipolar depression, five with bipolar depression, five with mania, three with mixed bipolar states and nine control subjects. Whole-brain glucose metabolic rate was decreased in bipolar depressed and mixed affective groups, with this change normalising in those groups on resolution of depression or mania. The unipolar depressed group showed a lower caudate:whole-brain ratio of metabolic rate when compared with normals and bipolar depressed. These data suggest, like the CBF studies with xenon (Uytdenhoef *et al*, 1987), that global hypometabolism in bipolar depressives may be state- rather than trait-dependent in view of the normalisation on elevation of mood.

Baxter *et al* (1989) further attempted to identify a metabolic profile common to three depressive subtypes. In a study of 10 unipolar depressives, 10 bipolar depressives, 24 patients with obsessive–compulsive disorder with ($n = 10$) or without ($n = 14$) depression, 6 bipolar manics and 12 normal controls they found a significant decrease in the ratio of glucose metabolic rate in the left dorsal anterolateral pre-frontal cortex to that in the whole hemisphere (ALPFC:Hem). Similar though less significant changes were observed in the right ALFPC. Twelve patients were rescanned after antidepressant medication, and percentage increase in the left ALPFC: Hem ratio correlated with clinical improvement. The authors concluded that the data suggested a left-ALPFC abnormality in depression.

In a hypothesis-led study, Post *et al* (1987) investigated glucose utilisation in the temporal lobes of 13 patients meeting DSM-III criteria for primary affective illness. Five patients were depressed, six 'improved' or euthymic, and two were hypomanic. Data were compared with those obtained from 18 normal volunteers and from 17 schizophrenics. A somatosensory paradigm was used to attempt to control for ambient conditions between patients and subjects, and regional values were normalised to the maximum value for the relevant PET scan slice. In the depressed group the right and left temporal lobes revealed a relative hypometabolism, reaching statistical significance only on the right.

These studies illustrate the need to study larger numbers of well defined patients longitudinally and the need to develop regionally specific activation paradigms before final conclusions are made about focal abnormalities in metabolism. Cross-sectional designs include, for example, comparing depressives with non-depressives and depressives with depressives. The former design has been employed extensively and may be of limited use, particularly with small patient samples. The problems in cross-sectional studies are even more striking in schizophrenia. Confounding differences between schizophrenics and normals are innumerable: some of the more important include taking large amounts of drugs, differences in social class, pre-morbid adjustment, highest educational level, number of years in hospital, hostility, suspiciousness, and arousal. Some of these variables have been shown to affect regional cerebral activity, and those which have not would probably be interesting experiments in themselves. The main findings of 'patient-normal' comparisons are 'hypofrontality' and altered cortico-subcortical metabolic gradients. Neither of these are specific to affective disorders or schizophrenia, as previously discussed.

In conclusion, PET studies of affectively ill patients have consistently found decreased cerebral metabolism, most frequently located to the inferior frontal lobe, during the depressed state. ROI analysis may limit the extent to which these changes can be related to anatomical or monoaminergic theories of affective illness. The development of pixel-by-pixel analysis in association with specific activation paradigms, neuropsychological and neuropharmacological, should increase the sensitivity of the technique and allow identification of anatomica regions of abnormality and covarying brain regions with an implicated relationship to connectivity an neural networks. The nosological status of clinicall identified subsyndromes can then be validated b relationship to PET-determined functional changes

Obsessional disorders

Obsessive-compulsive disorder (OCD) has traditionally been classified as a neurotic disorder, wit an assumed psychological aetiology. OCD is perhap the most disabling of the non-psychotic menta disorders and may occur in up to 1 in 200 teenager (Flament *et al*, 1988). It is characterised b unwanted, persistent, recurrent intrusive thought which may be accompanied by ritualistic behaviou or compulsions. The similarity between compulsiv behaviour and movement disorders has led to th hypothesis that OCD may be secondary to basal ganglia dysfunction. PET can test this hypothesi directly.

Baxter *et al* (1987) studied 14 patients with OC and compared them with 14 controls and 14 patient with unipolar depression. In OCD a significan elevation in metabolism was seen in the left orbita gyrus, with a non-significant elevation in the righ orbital gyrus, and significant elevations bilaterall in caudate nuclei. These findings were related t mental state in that the orbital gyrus metabolis remained elevated even after successful drug treatment, whereas the caudate: hemisphere metaboli ratio increased from a normal level in the morbi state to an elevated level with improvement o symptoms after drug treatment. The authors hypothesised from these findings that in symptomati OCD cortical activity, especially orbital, is elevate beyond the capacity of the caudate to maintain it integrative role; that is, orbital cortex is 'released' With successful treatment the caudate re-establishe its processing capacity through an increase in it metabolic rate relative to functionally connecte structures.

The limitations of this study in terms of heterogeneity of patient group were addressed subsequentl (Baxter *et al*, 1988), when drug-free, non-depressed right-handed patients with OCD were compared wit a new group of matched controls. Similar result were found, with globally raised cerebral metaboli rates in addition to bilaterally raised metabolism i caudate nuclei, orbital gyri and orbital: hemispher ratio. In the third study of this series (Baxter *et al* 1989) OCD patients with and without depressio were compared with unipolar and bipolar depressive and normal controls. In this study the OCD patient with depression had significantly lower metabolic rates in the left ALPFC compared with OCD patients without depression. This metabolic pattern was also found in the primary-depression groups.

Swedo *et al* (1989) studied 18 adults with OCD of childhood onset and 18 matched controls. This group found significantly increased bilateral pre-frontal, left orbital frontal, left pre-motor and right sensorimotor metabolism and increased bilateral anterior cingulate metabolism. Increased caudate metabolism did not reach significant levels. Metabolic measures correlated with measures of clinical state and predicted response to clomipramine, with non-responders having the highest metabolic rates.

Martinot *et al* (1989) examined the relationship between regional metabolism and clinical and neuropsychological features of OCD in 16 non-depressed patients and eight controls. In all brain regions absolute metabolic rates were significantly lower in patients than in controls, not explained by the effect of concurrent medication in 10 out of 16 of the patients. No relationship was found between metabolic rates and clinical data but neuropsychological data revealed significant impairment of the OCD group in memory and attention tasks. When related to regional metabolism, absolute metabolic rates for lateral pre-frontal areas and for whole cortex were inversely correlated to Stroop-test subscores.

A single study of Gilles de la Tourette syndrome, which is invariably associated with obsessional features, has also reported increased metabolism in the basal ganglia (Chase *et al*, 1984*b*).

Thus PET studies lend support to the hypothesis that OCD is associated with a functional abnormality in the basal ganglia and frontal cortex. Further studies are underway to assess metabolic rates before and after psychological and pharmacological treatment and will affect the nosological status of OCD, previously considered a neurotic disorder with a psychological aetiology.

Anxiety states and panic disorder

Anxiety states are the most common psychiatric disorders. Within this group of disorders, one in particular, panic disorder (PD), has caught the attention of 'biological' psychiatrists. PD is characterised by recurrent, discrete attacks of extreme anxiety in the absence of a frightening stimulus. In a substantial subgroup of patients with PD, infusion of sodium lactate precipitates an anxiety attack. This rarely happens in normal controls, suggesting a neurobiological basis for this problem.

Reiman *et al* (1984) studied ten patients with panic disorder (seven lactate responders) and six normal controls, using ^{15}O-labelled water to measure CBF. Patients were studied resting. There were no differences in global or hemispheric values between groups, but ROI analysis revealed a significantly decreased left-to-right ratio in the parahippocampal gyrus of the PD patients who were lactate responders. In a further study (Reiman *et al*, 1986), which included increased numbers of patients and controls, the previous finding of hippocampal asymmetry in lactate-sensitive patients was replicated using measures not only of blood flow but also of blood volume and oxygen metabolism. The lactate-sensitive PD patients also had raised whole-brain oxygen metabolism.

This series was further extended (Reiman *et al* 1989*a*,*b*) to include studies of patients during a discrete panic attack and of normal controls during states of anticipatory anxiety, awaiting an unpleasant electrical stimulus. These studies represent a significant advance in terms of the data-analysis technique (Fox *et al* 1988). Firstly, global blood flow was normalised to 50 ml/100 g/min. Secondly, the population of regional changes in blood flow, as determined from subtracted PET images (i.e. test state minus rest state), were examined statistically for significant change. Finally, locations of the rCBF changes were established with reference to the stereotactically standardised data matrix. In the first study, during a lactate-induced panic attack, there were significant increases in rCBF in the temporal poles, insular cortex, claustrum, lateral putamen, the vicinity of the superior colliculus and in the vicinity of the left anterior cerebellar vermis. In the second study, during production of anticipatory anxiety, there were significant increases in rCBF in identical regions. The authors suggested a final common pathway for the expression of these two forms of anxiety involving the temporal poles. These findings relate well to the theory of Gray (1982) which implicates the hippocampus and its afferent and efferent connections in the neurobiology of anxiety.

A single study from another centre (Mountz *et al*, 1989) compared seven subjects with simple phobias of small animals with eight normal controls. Each subject received five PET scans in a fear–rest–fear repeated-measures paradigm. Although phobic stimuli produced a significant increase in state anxiety during fear and significant differences in peripheral physiological measurements between the fear and rest scans, any changes in global or regional CBF were found to be non-significant when the effects of hypocapnia due to anxiety-induced hyperventilation were taken into account. In view of these results the authors suggested that CBF changes induced by state anxiety are either not measurable by PET techniques or else do not exist. They further concluded that the frequently voiced concerns of the confounding effect of subject anxiety on CBF measurements are overstated.

PET in neuropsychiatric disorders

Psychiatric morbidity is common in primary neurological illness. The presence of psychotic or non-psychotic symptoms in the presence of a demonstrable (focal) pathological process is clearly of great interest in the understanding of the generation of such symptoms. Earlier, restrictive approaches, in which disorders were thought to be either neurological (organic) or functional (psychiatric), have led to a limited understanding between the relationship of psychopathology and disturbance of regional brain function. PET studies have also been subject to this conflict of paradigms, with a few notable exceptions. The design of future PET activation studies will address similarities rather than differences between various neuropsychiatric disorders. A full review of PET in neuropsychiatric disorders is beyond the scope of this review: the following section illustrates the potential application of PET in neuropsychiatric research, with reference to two conditions, thalamic infarction and Parkinson's disease.

Thalamic infarction

Following isolated infarcts of the thalamus, a wide range of clinical manifestations are recognised. These include verbal and visual memory impairment, aphasia, neglect and behavioural change (Bogousslavsky *et al*, 1988). PET studies have shown that clinical symptoms in these patients seem to be the result of remote physiological effects rather than a direct consequence of the subcortical (thalamic) pathology. Baron *et al* (1986) described PET and neuropsychological findings in ten patients with unilateral vascular thalamic lesions demonstrated by CT. Neuropsychological testing focused on language and memory. Four patients were re-studied three to six months after the first study. In nine out of the ten patients there was significant ipsilateral cortical hypometabolism affecting the whole cortical mantle diffusely, this change tending to normalise with time after the stroke. A range of neuropsychological abnormalities were displayed in these patients, including language disturbance (incoherence, dysarthria, word-finding difficulties and impaired verbal fluency), memory impairment (visual and verbal memory) and disorientation for time and place. These findings also normalised with time. Kuwert *et al* (1989) demonstrated ipsilateral hypometabolic changes in five out of seven patients with unilateral thalamic infarcts. Areas affected included cerebellum (4/5), frontal cortex (3/5) and parietal cortex (5/5).

Parkinson's disease

Depressive symptoms are common in Parkinson's disease. The reported incidence varies between 40% and 50% (Schiffer *et al* 1988). The relationship between the two disorders is controversial, with the most frequently posited hypothesis being that depression is a psychological reaction to the motor disability. Brown & MacCarthy (1990) found an absence of somatic symptoms, negative self-referential ideation and suicidal thoughts or actions in a sample of patients with Parkinson's disease and suggested that this confirmed the more reactive nature of mood disturbance. Clinical impression, however, suggests that mood disorder may predate motor disorder in a significant number of cases. Mayberg *et al* (1989) investigated the relationship between mood disorder and cerebral glucose metabolism in eight patients with Parkinson's disease (three with major depression, two with minor depression and three non-depressed) and four normal volunteers. All patients were in the early stages of Parkinson's disease (Hoehn-Yahr scale range 1–3; North Western Disability Scale <14) and were cognitively normal as assessed by the Mini Mental State examination. Significant differences between the groups were seen, with hypometabolism in orbital and inferior prefrontal cortex in the depressed patients (major and minor depression) compared with non-depressed Parkinsonian and control subjects. Severity of depression correlated with metabolic rate. This finding suggests that a specific neurochemical abnormality may underly this feature of Parkinson's disease, perhaps loss of extrastriatal ascending monoaminergic pathways. This has validity in terms of the previously discussed primate studies in which lesions of such pathways are associated with decreased frontal metabolism.

Conclusions

Positron emission tomography is the most powerful technique available for the investigation of brain function *in vivo*. The task of research workers is further refinement of the methodology involved, particularly in the fields of design of activation paradigms and data analysis, which will further increase the sensitivity and specificity of the method. To date, the majority of studies of patients with psychiatric disorders have been in the resting state. Regional abnormalities have been consistently found in the major psychoses and there is some evidence for abnormalities specific to two neurotic disorders traditionally thought to have a psychological aetiology, namely panic disorder and obsessive-compulsive disorder. Future PET programmes will couple metabolic measures with pharmacological and cognitive activation of specific functional systems and studies using tracers for neuroreceptors will attempt to provide a parallel neurochemical basis for the metabolic profiles. In conjunction with delineation of clinical subsyndromes, these techniques should lead to significant advances in the understanding of the pathophysiology of the major psychoses.

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Cognitive Brain Potentials and their Application

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Computerised averaging methods have made it possible to extract and identify the electrical activity accompanying specific activities of the brain, including certain psychological processes, from the random background signals in electroencephalography (EEG). Event-related potentials (ERPs) and the way these change under various recording conditions are a powerful, non-invasive and relatively simple means of relating psychopathology to underlying physiology, and by comparing ERPs with imaging data it should be possible to compare electrical activity with changes in brain structure and blood flow in different disease states.

As the name suggests, event-related potentials are very small voltages generated in brain structures in response to specific events or stimuli. These tiny time-locked potentials are selected from the ongoing EEG activity by averaging epochs of EEG following repeated sensory stimuli such as a series of clicks or flashes of light.

It takes about 20 ms for information to reach the cortex from a peripheral sense organ, so early ERPs generated within this time mainly reflect neuronal activity in the sensory organ itself and in the afferent pathways of the brain-stem. For example, during the first 10 ms following a click, ERPs recorded from the scalp include five peaks representing neuronal activity in the acoustic nerve, cochlea nucleus, superior olive, lateral lemniscus and inferior colliculus (Jewett & Williston, 1971). Similar series of early event-related potentials are generated in the optic pathways following a flash of light and in the spinal cord and sensory afferent pathways of the brain-stem following a somatosensory stimulus. These early responses are termed 'exogenous' because they are generated regardless of what the subject is thinking, and they are quite independent of any response the subject may subsequently make to the stimulus. They are extremely useful clinically for detecting disorders of sensory end organs and the brain-stem, and are routinely used in audiology clinics and in the assessment of brain injury and coma (Halliday, 1982; Chiappa, 1983).

In contrast to these exogenous potentials, ERPs generated after about 70 ms often reflect the manner in which a stimulus is evaluated by the subject. These later components are termed 'cognitive' or 'endogenous' ERPs because their amplitude and latency may depend on the motivation of the subject and the cognitive, affective or motor response to that particular stimulus. One of the first observations of an endogenous potential was by Grey *et al* (1964), who described the contingent negative variation (CNV) or expectancy wave elicited during a test in which the subject heard a warning click followed three seconds later by a light flash and a button-press response to this. Immediately after the warning click a negative potential could be recorded from scalp electrodes and this CNV steadily increased in amplitude between the two signals, then resolved once the response (button press) had been performed. The CNV, which is now believed to incorporate more than one component, seems to reflect neuronal activity connected with the appreciation of the significance of the incoming signal and the preparation by the subject of a goal-directed act.

At about the same time Sutton *et al* (1965) described another late endogenous response, the P300, generated during the performance of a task which required the resolution of uncertainty. During this 'odd-ball' task, the subject is exposed to two different stimuli (e.g. a high-pitched and a low-pitched tone), one of which occurs relatively infrequently and is designated as a 'target'. When the subject's attention is directed to the target by counting or pressing a button, a positive potential is generated some 300 ms after this signal. This P300 response occurs with auditory, visual and somatosensory stimuli, and like the CNV it is relatively independent of the physical characteristics of the stimulus itself. A P300 response can be generated in the absence of a stimulus when there is a gap in an otherwise continuous series of sounds or flashes of light, which is evidence that this ERP is a reflection of mental activity and not merely a response to the stimulus itself.

The very large literature on P300 (Regan, 1989) has addressed but not yet resolved the question of which cognitive processes contribute to the generation of the P300 wave form. The latency of P300 increases with the difficulty of the task required of the subject (e.g. having to distinguish three tones rather than two tones will increase the latency). The amplitude of P300 increases with the unexpectedness of the target tone (Hillyard & Picton, 1987). The P300 is thought to be a complex mixture of at least three wave forms

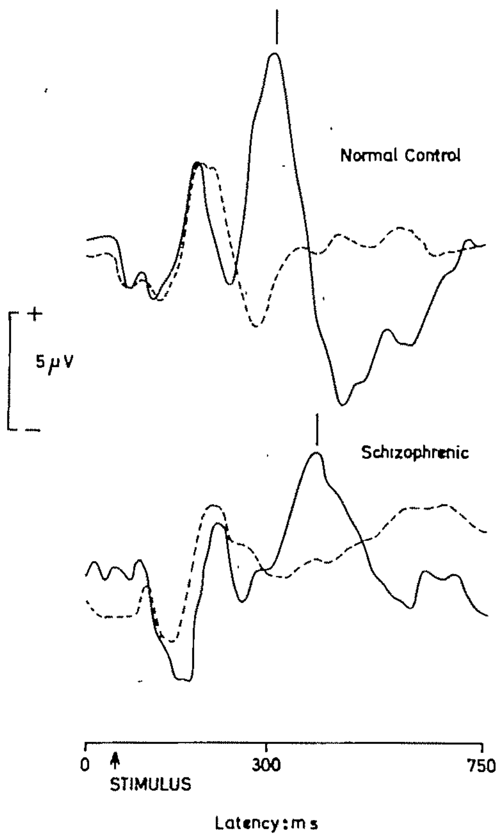

FIG. 1 The upper trace illustrates a P300 response recorded from a normal control subject during the performance of an 'odd-ball' test. The subject was asked to count infrequent high-pitched tones (1500 Hz) randomly embedded in a series of low-pitched tones (1000 Hz). The averaged EEG response recorded from the vertex over 750 ms is shown by the dotted line and includes a negative deflection at around 100 ms (N1) and a positive wave at about 200 ms (P2). The continuous line is the averaged response to the high-pitched 'target' tones and includes a large positive potential at 300 ms (P300) preceded by a negative deflection (N2). The lower trace recorded from a drug-free schizophrenic subject illustrates reduced amplitude and delayed latency of P300, such as is frequently found in schizophrenia and in several forms of dementia.

and these, together with the N1, P2 and N2 waves which precede it (see Fig. 1), probably reflect various aspects of information processing required for the recognition, retrieval from memory and judgements about the significance of a signal. Overall the P300 seems to reflect mental processes that allow us to anticipate significant events in our environment and to react to unexpected changes. Recognising a familiar face in a crowd or being alerted by a slight change in frequency or loudness of a previously regular sound (e.g. a ticking clock) are probably everyday examples of an 'odd-ball' response. It was therefore an obvious step to record these late endogenous ERPs, including the P300, in psychiatric patients with conditions such as dementia, depression and schizophrenia, which are associated with disordered attention, since ERPs might contribute to diagnosis and provide a method for monitoring cognitive change in response to specific treatments. Figure 1 illustrates the P300 response in a control subject and a schizophrenic.

ERPs in dementia

Goodin *et al* (1978) were the first to investigate P300 as a measure of cognitive function in dementia. Twenty-seven demented patients (9 with pre-senile dementia and 18 with a wide variety of diagnoses including metabolic encephalopathies) were compared with non-demented neurological and psychiatric patients and a third group of normal controls. Dementia, even in this mixed group of diagnoses, was associated with reduced amplitude and increased latency of P300 using an auditory odd-ball paradigm. Many studies have confirmed these initial findings (Pfefferbaum *et al*, 1984; St Clair *et al*, 1985; Gordon *et al*, 1986; Neshige *et al*, 1988). Polich *et al* (1986), also studying a diagnostically mixed group of dementia patients (including Alzheimer's disease, alcohol dementia, vascular disease and other diagnoses), reported a direct association between P300 latency and the degree of cognitive impairment. However, there are weaknesses in studies of mixed groups of dementia patients since correlations between P300 latency and specific memory deficits may depend on diagnosis and are, for example, different in Alzheimer's compared with Korsakoff patients (Blackwood *et al*, 1987*a*).

Subtypes of dementia distinguished by P300

By recording P300 in carefully defined groups of demented patients some interesting results have emerged suggesting that P300 may show different patterns of change in different diseases. St Clair *et al* (1985) recorded auditory P300 from a group of patients meeting strict diagnostic criteria for Alzheimer's dementia, a group with alcoholic Korsakoff's syndrome, and normal controls. The Alzheimer's patients had delayed latency and reduced amplitude of P300, but surprisingly the Korsakoff's group as a whole did not differ significantly from controls, despite showing very severe memory disturbance.

Goodin & Aminoff (1986) recorded auditory ERPs from 22 subjects meeting strict criteria for Alzheimer-type dementia, 13 patients with Huntington's disease, and 13 patients with dementia associated with Parkinson's disease. The results were compared with those from a normal control group, and the analysis included four potentials, the N1, P2, N2 and P300 wave forms recorded from the vertex. Not only did the three patient groups differ significantly from controls, but ERP latencies and amplitudes could distinguish between the three types of dementia. The ERP changes were judged to be secondary to the dementing process since asymptomatic but 'at-risk' members of Huntington's families and non-dementing Parkinson's patients had normal ERPs. In all demented groups the peaks of N2 and P300 occurred much later than in normal controls. The Huntington's and Parkinson's demented groups (classified by the authors as having 'subcortical' dementia) differed from the Alzheimer's group (classified as 'cortical' dementia) in showing a greater degree of N2 and P300 prolongation and by greater latency of the earlier N1 and P2 components. In Huntington's disease the changes in P2 were significantly greater than in Parkinson's disease. Hence all three diagnostic groups could be classified with reasonable accuracy on the basis of ERPs.

Changes in ERPs suggestive of both 'cortical' and 'subcortical' dementia have recently been reported in patients infected with HIV (Goodin *et al*, 1990). Changes were particularly marked in patients showing signs of dementia, but 28% of non-demented patients also had a longer latency period in at least one ERP component, leading the authors to propose that ERP may be useful in the early detection of AIDS dementia and for the selection of patients for specific drug treatments. Serial recording of ERP latencies could be used to follow the progress of the disease and to monitor the response to treatment.

The P300 response has also been shown to change with the onset of Alzheimer-type dementia when it occurs in subjects with Down's syndrome in middle age. In Down's syndrome the behavioural and cognitive changes of dementia are accompanied by increased P300 latency and reduced P300 amplitude, and these changes could be useful in the early detection of dementia and the measurement of its course (Blackwood *et al*, 1988; Muir *et al*, 1988).

The effect of pharmacological interventions on auditory P300 has been examined in both Parkinson's disease and Alzheimer's dementia. Parkinson's patients have a shorter P300 latency during their 'on-phase' as opposed to their 'off-phase' (Starkstein *et al*, 1989), supporting the notion that auditory P300 latency may reflect the activity of dopaminergic systems in the brain. In visual pathways also, Bodis-Wollner *et al* (1982) had demonstrated that delayed ERPs in Parkinson's disease could be modified by treatment with *l*-DOPA.

However, changes in other neurotransmitter systems may also affect the auditory P300. The destruction of ascending noradrenergic fibres by lesions of the locus ceruleus alters the scalp-recorded P300 in monkeys (Pineda *et al*, 1989), and P300 latency is increased following the administration of the muscarinic antagonist scopolamine to control subjects (Callaway, 1983). Surprisingly, in patients with Alzheimer's dementia an infusion of the cholinomimetic drug physostigmine had no effect in reducing the abnormally delayed P300 (Blackwood & Christie, 1986), suggesting that the pharmacology of P300 may vary in different disease states.

P300 in schizophrenia and depression

Pfefferbaum *et al* (1984) compared P300 in dementia, schizophrenia and depression. Patients with schizophrenia, like the dementia group, had an increased latency and a reduced amplitude of the auditory P300, while the depressed group did not differ from controls. Other studies have confirmed that P300 latency and amplitude could help to distinguish depression from dementia (Goodin *et al*, 1978; Gordon *et al*, 1986) and changes in P300 and other long-latency ERPs, especially those which reflect selective attention (Barrett *et al*, 1986), are now well established in schizophrenia. A reduction in P300 amplitude during auditory detection tasks has been reported in schizophrenia (Roth & Cannon, 1972; Shagass *et al*, 1977, 1978; Verleger & Cohen, 1978; Levit *et al*, 1973; Baribeau-Braun *et al*, 1983; Morstyn *et al*, 1983; Pfefferbaum *et al*, 1984; Blackwood *et al*, 1987*b*; Romani *et al*, 1987), in schizophrenic children (Erwin *et al*, 1986) and in relatives of schizophrenic subjects (Saitoh *et al*, 1984; Blackwood *et al*, 1990). A number of studies have also found that P300 latency is increased in schizophrenia (Pfefferbaum *et al*, 1984; Blackwood *et al*, 1987*b*; Romani *et al*, 1987; Ebmeier *et al*, 1989) although this has not always been found, possibly owing to variation in P300 recording techniques. In particular, the choice of low band-pass filter may affect P300 latency and an increase in P300 latency in schizophrenia has been reported only in studies where a band-pass frequency of 0.5 Hz or above has been employed (Ebmeier *et al*, 1989; Selzer & Asbury, 1990).

The abnormal P300 response in schizophrenia may be useful as a physiological marker which could help to define the clinical boundaries of the schizophrenia spectrum. P300 latency appears to be independent of the effects of medication and clinical state since there was no apparent change in the P300 first recorded from patients when acutely psychotic and drug free and then retested several months later when on medication and relatively free from psychotic symptoms (Blackwood *et al*, 1987*b*). P300 changes similar to those in schizophrenia have been found in subjects with borderline/schizotypal personality disorder (Blackwood *et al*, 1986; Kutcher *et al*, 1987) and in a study of large multiply affected schizophrenic pedigrees, abnormalities of P300 latency and amplitude were found in relatives of schizophrenic probands, including many relatives who were entirely free of symptoms (Blackwood *et al*, 1990). These results suggest that along with other measures such as abnormal eye-tracking responses (Holzman *et al*, 1974; Matthysse *et al*, 1986) P300 changes may be a useful vulnerability trait marker in schizophrenic families.

Another candidate vulnerability trait that appears to show consistent impairment in unmedicated and medicated schizophrenics is the P50 component of the auditory event-related response following the presentation of paired clicks. In normal subjects this scalp-recorded response some 50 ms after the stimulus is much reduced in amplitude following the second compared with the first click. Among schizophrenics little or no reduction occurs and this has been interpreted as an impaired ability to selectively filter incoming information (Adler *et al*, 1982; Freedman *et al*, 1983). A disorder of P50 habituation is also present among relatives of schizophrenic subjects. Siegel *et al* (1984) studied 14 first-degree relatives in nine families of schizophrenic probands and reported loss of P50 habituation in approximately half of the siblings and usually one parent of each proband. They suggest it may be a trait marker for schizophrenia which is also associated with other alterations in event-related potentials, including a reduced N100 and P200 amplitude (Freedman *et al*, 1987; Waldo *et al*, 1988).

It is clear that several components of event-related potentials are abnormal in schizophrenia. Another example is the auditory P200 component, the positive potential some 200 ms after a single stimulus, which is of lower amplitude in schizophrenics compared with controls (Jones & Callaway, 1970; Saletu *et al*, 1971; Roth & Cannon, 1972; Roth *et al*, 1980; Pfefferbaum *et al*, 1984; Shenton *et al*, 1989).

These ERP findings suggest that several aspects of information processing are disordered in schizophrenia, but it is not clear how these physiological changes relate to underlying pathology. Romani *et al* (1987) performed computerised tomography scans and recorded auditory P300 on 20 schizophrenic subjects. Although the schizophrenic group had enlarged ventricles and P300 responses differing in latency and amplitude from controls, there was no consistent association between P300 changes and ventricular size. McCarley *et al* (1989) reported that P300 amplitude reduction in schizophrenia was significantly correlated with enlargement of the left Sylvian fissure and with ratings for positive symptoms in schizophrenia.

Conclusions

Event-related potentials are easy to record using procedures which are well tolerated by quite disturbed patients. They are non-invasive and evidence to date would suggest that changes in components of endogenous ERPs may be useful in studying dementias and as biological markers for schizophrenia, providing a means for defining schizophrenia-spectrum disorders. It is a further possibility that studies using magnetic resonance imaging or measurements of cerebral blood flow will reveal the anatomical and neuropathological changes which give rise to the ERP amplitude and latency shifts, thus linking brain pathology with disorders of specific aspects of information processing.

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INDEX TO VOLUME 148

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INDEX TO VOLUME 148

PART I—SUBJECTS 1–10
PART II—CONTRIBUTORS 10–17
PART III—BOOK REVIEWS 17–19
ACKNOWLEDGEMENT TO ASSESSORS 20

Index to Volume 148

PART I—SUBJECTS

Compiled by A. S. Thorley

Abbreviation: C—Correspondence

Adaptation, psychological: The epidemiology of life events and long-term difficulties, with some reflections on the concept of independence; P. Mc C. Miller *et al* 686–696

Affective disorders: Affective disorder amongst women in the general population: a longitudinal study; P. G. Surtees *et al* 176–186

Early life events and affective disorder revisited; C. Faravelli *et al* 288–295

Political hazards in the diagnosis of 'sluggish schizophrenia'; Harold Merskey and Bronislava Shafran 247–256

Multivariate investigation of post-partum mood disturbance; P. R. Gard *et al* 567–575

Seasonal affective disorder; J. R. King (C) 478. Reply; Norman E. Rosenthal and Steven P. James (C) 478–479

Utility of a single-point dosing protocol for predicting steady-state lithium levels; Paul J. Perry *et al* 401–405

Affective symptoms: Impact of individual and family treatment on the affective climate of families of schizophrenics; Jeri A. Doane *et al* 279–287

Aged (65 yrs and over): Computed tomography in the elderly: changes over time in a normal population; Jonathan M. Bird *et al* 80–85

Electrocardiogram changes and therapeutic desipramine and 2-hydroxy-desipramine concentrations in elderly depressives; S. P. Kutcher *et al* 676–679

Alcohol drinking: Blood alcohol survey in patients with self-poisoning; R. Varadaraj and J. D. Mendonca (C) 615

Alcoholism: Alcoholism and the general practitioner; Alison Mowbray and Neil Kessel 697–700

At risk drinking among general practice attenders: prevalence, characteristics and alcohol-related problems; Michael King 533–540

Minimal sedation required with nitrous oxide-oxygen treatment of the alcohol withdrawal state; M. A. Gillman and F. J. Lichtigfeld (*Brief report*) 604–606

Psychiatric disorder, drinking and alcoholism: what are the links? Morris W. Bernadt and Robin M. Murray 393–400

Relationship between alcoholism and neurosis: evidence from a twin study; M. J. Mullan *et al* 435–441

Women, life events and drinking problems; Carole A. Allan and D. Cooke (*Comment*) *462*

Alzheimer's disease: Clinical tests of memory; Michael D. Kopelman 517–525

AMDP-system (*Arbeitsgeminschaft für Methodik und Dokumentation in der Psychiatrie*). The AMDP system in clinical psychopharmacology; D. Robon and B. Woggon (*Brief report*) 467–468

Amino acids: Plasma amino acids, Down's syndrome and dementia; Sarah E. Watkins *et al* (C) 339–340

Amitriptyline: Imipramine and amitriptyline plasma concentrations and clinical response in major depression; James H. Kocsis *et al* 52–57

Anniversary reactions: Anniversary reactions; E. B. Renvoize and J. Jain (*Brief report*) 322–324. John Birtchnell (C) 610–611

Annotations: Model of brain function: its implications for psychiatric research; Bruce E. Wexler 357–362

Treatment of prolonged combat reaction: A. Bleich *et al* 493–496

Anorexia nervosa: Anorexia nervosa; drop-outs from treatment; Maurice Silverman (C) 108

Measurement of body image disturbances in anorexia nervosa; experimental comparison of different methods; Manfred M. Fichter *et al* 453–461

Anorgasmia: Cyproheptadine and anti-depressant-induced anorgasmia; Alan J. Riley and Elizabeth J. Riley (C) 217–218

Antidepressive agents: Comparative effects of seven anti-depressant regimes on appetite, weight and carbohydrate preference; Brian Harris *et al* (*Brief report*) 590–592

Cyproheptadine and antidepressant-induced anorgasmia; Alan J. Riley and Elizabeth J. Riley (C) 217–218

Antidepressive agents, tricyclic: Adverse drug reactions to first- and second-generation antidepressants: a critical evaluation of drug surveillance data; L. G. Schmidt *et al* 38–45

Apomorphine: Effects of intravenous and subcutaneous administration of apomorphine on the clinical symptoms of chronic schizophrenia; E. K. G. Syvälakti *et al* 204–208

Appetite disorders: Comparative effects of seven anti-depressant regimes on appetite, weight and carbohydrate preference; Brian Harris *et al* (*Brief report*) 590–592

Asperger's syndrome: Asperger's syndrome and Tourette syndrome: the case of the pinball wizard; Jacob Kerbeshian and Larry Burd (*Brief report*) 731–736

Is there a right-hemisphere dysfunction in Asperger's syndrome?; J. de Leon Molina *et al* (C) 745–746

Asylum: The discovery of the asylum; David J. Rothman; J. L. T. Birley (*Books reconsidered*) 330–331

Attention: Brain indicators of altered attention and information processing in schizophrenic patients; K. Barrett *et al* 414–420

Attitude of health personnel: Development of scales to measure treatment attitudes in psychiatry; Greg Wilkinson and Paul Williams 581–586

Behçet's syndrome: Psychiatric manifestation as an early symptom of Behçet's disease; Shigeru Chiba *et al* (C) 752–753

Benzodiazepines: Schneiderian first rank symptoms caused by benzodiazepine withdrawal; Keith Roberts and Neil Vass (*Brief report*) 593–594

LIBRARY
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Bereavement: Mania following bereavement: a case report; Stephen J. Rosenman and Helen Tayler (*Brief report*) 468–470

Body image: The measurement of body image disturbances in anorexia nervosa: experimental comparison of different methods; Manfred M. Fichter *et al* 453–461

Body weight: Comparative effects of seven antidepressant regimes on appetite, weight and carbohydrate preference; Brian Harris *et al* (*Brief report*) 590–592

***Books reconsidered:** The Discovery of the Asylum;* David J. Rothman; J. L. T. Birley 330–331

Botswana: The prevalence of schizophrenia in a remote area of Botswana; David I. Ben Tovim and Josephine M. Cushnie 576–580

Brain: Conversion, paranoia and brain dysfunction; Laurence Miller (C) 481

Is there a right-hemisphere dysfunction in Asperger's syndrome?; J. de Leon Molina *et al* (C) 745–746

Mindlessness and brainlessness in psychiatry; Leon Eisenberg (*Eli Lilly Lecture 1986*) 497–508

Model of brain function: its implications for psychiatric research; Bruce E. Wexler (*Annotation*) 357–362

Bleuler, E.: Epilepsy, psychosis, Kraepelin and Bleuler; Cornelia Thiels (C) 107–108

Brazil: Validity study of a psychiatric screening questionnaire (SRQ–20) in primary care in the city of São Paulo; Jair de Jesus Mari and Paul Williams 23–26

Bulimia nervosa: Depressive symptoms of bulimia nervosa; Peter J. Cooper and Christopher G. Fairburn 268–274

Thirty month follow-up of cognitive-behavioural group therapy for bulimia; Laszlo P. Luka *et al* (C) 614–615

Brief reports: AMDP-system in clinical psychopharmacology; D. Bobon and B. Woggon 467–468

Anniversary reactions; E. B. Renvoize and J. Jain 322–324

Asperger's syndrome and Tourette syndrome; the case of the pinball wizard; Jacob Kerbeshian and Larry Burd 731–736

Case of parietal lobe atrophy; Paul Dedman and Sharon Numa 725–726

Clovoxamine and doxepin in major depressive disorder: a double-blind controlled trial; G. J. Lodge and Hugh L. Freeman 718–721

Comparative effects of seven antidepressant regimes on appetite, weight and carbohydrate preference; Brian Harris *et al* 590–592

Comparison of the prophylactic action of flupenthixol with placebo in lithium treated marine-depressive patients; J. Esparon *et al* 723–725

Does viloxazine really improve sex drive? A double-blind controlled study; Diego De Leo and Guido Magni 597–599

Evolution of variants of the Munchausen syndrome; Kenneth Sinanan and Helen Haughton 465–467

Folie à deux in identical twins: interaction of nature and nurture; Arthur Lazarus 324–326

49, XXXXY chromosome anomaly: an unusual variant of Klinefelter's syndrome; T. Hari Singh and Sudhir Rajkowa 209–210

49, XXXYY chromosome anomaly in a mentally retarded man; Valerie A. Cowie *et al* 210–212

Gilles de la Tourette's syndrome in Down's syndrome—a case report; H. Karlinsky *et al* 601–604

Grade scores of the Montgomery-Åsberg Depression and Clinical Anxiety scales; R. P. Snaith *et al* 599–601

Hypomania following cognitive therapy; David Kingdon *et al* 103–104

Koro—a psychophysiological dysfunction?; F. Oyebode *et al* 212–214

Late-onset folie simultanée in a pair of monozygotic twins; Kenneth Kendler *et al* 463–465

Lithium augmentation in the treatment of delusional depression; M. Pai *et al* 736–738

Locus of control in short and long sleepers; Anand Kumar and A. K. Vaidya 739–740

Mania following bereavement: a case report; Stephen J. Rosenman and Helen Tayler 468–470

Manic depressive psychosis in a mentally handicapped person—diagnosis and management; S. R. Kadambari 595–596

Minimal sedation required with nitrous oxide-oxygen treatment of the alcohol withdrawal state; M. A. Gillman and F. J. Lichtigfeld 604–606

Normal dexamethasone suppression test in obsessive-compulsive disorder; W. Monteiro *et al* 326–329

One hundred cases of hysteria in Eastern Libya: a socio-demographic study; Tinnyunt Pu *et al* 606–609

Prolactin response induced by ECT and TRH; Yiannis Papakostas *et al* 721–723

Schneiderian first rank symptoms caused by benzodiazepine withdrawal; Keith Roberts and Neil Vass 593–594

Short term intensive psychotherapy—a case history; Richard Gillett 98–100

True auditory hallucinations as a conversion symptom; Chittaranjan Andrade and Shoba Srinath 100–102

Unpredictability as a correlate of expressed emotion in the relatives of schizophrenics; B. MacCarthy *et al* 727–731

Catatonia: Neuroleptic malignant syndrome and lethal catatonia; James Lindsay (C) 342–343

Capgras syndrome: Capgras syndrome; Anthony B. Joseph (C) 749–750. A. Schofield (C) 750. Laurence Jerome (C) 751

Cerebral ventricles: Hypothyroidism as a correlate of lateral ventricular enlargement in manic-depressive and neurotic illness; Eve C. Johnstone *et al* 317–321

Ventricular size and CSF transmitter metabolite concentrations in severe endogenous depression; H. M. A. S. Standish-Barry *et al* 386–392

Cerebrovascular disorders: Depression influences intellectual impairment in stroke patients; Robert G. Robinson *et al* 541–547

China: Psychiatry in the People's Republic of China; William Ll Parry-Jones 632–641

Chromosome abnormalities: 49, XXXXY chromosome anomaly: an unusual variant of Klinefelter's syndrome; T. Hari Singh and Sudhir Rajkowa (*Brief report*) 209–210

49, XXXYY chromosome anomaly in a mentally retarded man; Valerie A. Cowie *et al* (*Brief report*) 210–212. Tom Thumb; Eric W. Fine (C) 753

Clinical Anxiety Scale: Grade scores of the Montgomery-Åsberg Depression and the Clinical Anxiety scales; R. P. Snaith *et al* (*Brief report*) 599–601

Clovoxamine: Clovoxamine and doxepin in major depressive disorder: a double-blind controlled trial; G. J. Lodge and Hugh L. Freeman (*Brief report*) 718–721

Cognition disorders: Macrocytosis and cognitive decline in Down's syndrome; R. W. Lansdall Welfare and K. E. Hewitt (C) 482–483

Combat disorders: Treatment of prolonged combat reaction: A Bleich *et al* (*Annotation*) 493–496

Comments: Causal models in psychiatric research; Matthew J. Edlund 713–717

Positive and negative symptoms in psychiatry; Michael R. Trimble 587–589

Should plasma or urinary MHPG be measured in psychiatric research? A critical comment; Johannes G. Eilser *et al* 95–97

Women, life events and drinking problems; Carole A. Allan and D. Cooke 462

Commitment: Outcome of patients committed to hospital under the Mental Health (Scotland) Act 1960; A. A. McKechnie *et al* 33–37

Community psychiatry: Self-esteem, vulnerability and psychiatric disorder in the community; J. G. Ingham *et al* 375–385

Conversion disorder: Conversion, paranoia and brain dysfunction; Laurence Miller (C) 481

Conversion without hysteria: a case report and review of the literature; Arieh Shalev and Hanan Munitz 198–203

Corrections: Body image distortion in bulimia nervosa; J. Birtchnell *et al* 219

Index to Volume 147, July–December 1985, page 4. Dupuytren's contracture 344

Cortisol: Depression, urinary free cortisol excretion and lymphocyte function; Ziad Kronfol *et al* 70–73

Depression and urinary free cortisol; Bernard J. Carroll (C) 218. S. P. Calloway and R. J. Dolan (C) 611

Raised plasma cortisol concentrations a feature of drug-free psychotics and not specific for depression; J. E. Christie *et al* 58–65

Crighton Royal Institution: *A hundred years ago;* Henry Rollin 197

Cross-cultural comparison: Cross-national invariance of dimensions of parental rearing behaviour: Comparison of psychometric data of Swedish depressives and healthy subjects with Dutch Target Ratings on the EMBU; Willem A. Arrindell *et al* 305–309

Ethnic differences in self-poisoning: a comparison of Asian and White groups; John Merrill and John Owens 708–712

Neuroleptics in culture-bound syndromes; Philip E. Harrison-Read (C) 106–109

Phobic neuroses in India: a cross-cultural comparison; M. S. Keshavan *et al* (C) 341–342

Transcultural psychiatry; Roland Littlewood (C) 340–341

Cyproheptadine: Cyproheptadine and antidepressant-induced anorgasmia; Alan J. Riley and Elizabeth J. Riley (C) 217–218

Day care: Day and full time psychiatric treatment; Ian A. Davidson and Dominic F. Connolly (C) 477. Reply; Peter H. Dick (C) 477–478

Death rate: Mortality and facial dyskinesia; H. A. McClelland *et al* 310–316

Delusions: Electroconvulsive therapy as a contributor to the production of delusional misidentification; George G. Hay 667–669

Dementia: Depression influences intellectual impairment in stroke patients; Robert G. Robinson *et al* 541–547

Folate deficiency in dementia; M. T. Abou-Saleh *et al* (C) 336–337. Gregory O'Brien and Andrew Clark (C) 337

Diagnostic criteria for dementia in DSM-III; Helen Christensen and Peter Birrell (C) 480–481

Huntington's chorea without dementia; O. W. J. Quarrell and Peter S. Harper (C) 612–613

Plasma amino acids, Down's syndrome and dementia; Sarah E. Watkins *et al* (C) 339–340

Depressive disorder: Awake, perchance asleep?; S. E. Southmayd *et al* (C) 748–749

Clinical tests of memory; Michael D. Kopelman 517–525

Cross-national invariance of dimensions of parental rearing behaviour: comparison of psychotic data of Swedish depressives and healthy subjects with Dutch target ratings on the EMBU; Willem A. Arrindell *et al* 305–309

Depression: distress or disease; Paul Bebbington (C) 479

Depression, hopelessness and suicide in chronic schizophrenia; Robert E. Drake and Paul G. Cotton 554–559

Depression influences intellectual impairment in stroke patients; Robert G. Robinson *et al* 541–547

Depression in general practice; C. V. R. Blacker and A. W. Clare (C) 334. Reply; L. I. Sireling and E. S. Paykel (C) 334–335. T. J. Fahy (C) 746–747

Depression in school phobia; Warren Weinberg *et al* (C) 335. Leslie Atkinson (C) 335–336

Depressive symptoms of bulimia nervosa; Peter J. Cooper and Christopher G. Fairburn 268–274

Diagnostic significance of vegetative symptoms in depression; Jonathan Davidson and Craig D. Turnbull 442–446

Endogenous sub-type of depression: a study of its internal construct validity; Michael A. Young *et al* 257–267

Levels of expressed emotion and relapse in depressed patients; Jill M. Hooley *et al* 642–647

Parental loss by death in the early childhood of depressed patients and of their healthy siblings; C. Perris *et al* 165–169

Perceived depriving parental rearing and depression; C. Perris *et al* 170–175

Psycho-social predictors of chronicity in depressed patients; R. M. A. Hirschfeld *et al* 648–654

Depressive disorder, drug therapy: Clovoxamine and doxapin in major depressive disorder: a double-blind controlled trial; G. J. Lodge and Hugh L. Freeman (*Brief report*) 718–721

Imipramine and amitriptyline plasma concentrations and clinical response in major depression; James H. Kocsis *et al* 52–57

Lithium in resistant depression; Samuel I. Cohen and B. A. Johnson (C) 219

Lithium augmentation in the treatment of delusional depression; M. Pai *et al* (*Brief report*) 736–738

Depressive disorder, physiopathology: Depression, urinary free cortisol excretion and lymphocyte function; Ziad Kronfol *et al* 70–73

Depression and urinary free cortisol; Bernard J. Carroll (C) 218. S. P. Calloway and R. J. Dolan (C) 611

Dexamethasone suppression test: fact and artefact; Louise Braddock (*Review article*) 363–374

Electrocardiogram changes and therapeutic desipramine and 2-hydroxy-desipramine concentrations in elderly depressives: S. P. Kutcher *et al* 676–679

Raised plasma cortisol concentrations a feature of drug-free psychotics and not specific for depression; J. E. Christie *et al* 58–65

Ventricular size and CSF transmitter metabolite concentrations in severe endogenous depression; H. M. A. S. Standish-Barry *et al* 386–392

Desipramine: Electrocardiogram changes and therapeutic desipramine and 2-hydroxy-desipramine concentrations in elderly depressives; S. P. Kutcher *et al* 676–679

Dexamethasone: Dexamethasone concentrations and the dexamethasone suppression test in psychiatric disorders; Howard Morris *et al* 66–69

Dexamethasone suppression test: fact and artefact; Louise Braddock (*Review article*) 363–364

Normal dexamethasone suppression test in obsessive-compulsive disorder; W. Monteiro *et al* (*Brief report*) 326–329

Diet: A double-blind gluten-free/gluten-load controlled trial in a secure ward population; Dimitrios N. Vlissides *et al* 447–452

Disability evaluation: The evaluation of illness behaviour and exaggeration of disability; J. R. Clayer *et al* 296–299

Diseases in twins: Folie à deux in identical twins: interaction. of nature and nurture; Arthur Lazarus (*Brief report*) 324–326

Homosexuality in monozygotic twins reared apart; Elke D. Eckert *et al* 421–425

Late-onset folie simultanée in a pair of monozygotic twins; Kenneth Kendler *et al* (*Brief report*) 463–465

Relationship between alcoholism and neurosis: evidence from a twin study; M. J. Mullan *et al* 435–441

Dominance—subordination: Dominance hierarchies in psychotherapy groups; James L. Kennedy and K. Roy Mackenzie (*Annotation*) 625–631

Down's syndrome: Gilles de la Tourette's syndrome in Down's syndrome—a case report; H. Karlinsky *et al* (*Brief report*) 601–604

Is mania really incompatible with Down's syndrome?; Iqbal Singh and G. Zolese (C) 613–614

Macrocytosis and cognitive decline in Down's syndrome; R. W. Lansdall Welfare and K. E. Hewitt (C) 482–483

Plasma amino acids, Down's syndrome and dementia; Sarah E. Watkins *et al* (C) 339–340

Doxepin: Clovoxamine and doxepin in major depressive disorder: a double-blind controlled trial; G. J. Lodge and Hugh L. Freeman (*Brief report*) 718–721

Drug administration schedule: Pharmacokinetics and therapeutic efficacy of haloperidol decanoate after loading dose administration; H. De Cuyper *et al* 560–566

Utility of a single-point dosing protocol for predicting steady-state lithium levels; Paul J. Berry *et al* 401–405

Drug dependence: A comparison of drug-related problems in London Accident and Emergency departments 1975–1982; Hamid Ghodse *et al* 658–662

Drug evaluation: Adverse drug reactions to first- and second-generation antidepressants: a critical evaluation of drug surveillance data; L. G. Schmidt *et al* 38–43

DSM-III: Diagnostic criteria for dementia in DSM III; Helen Christensen and Peter Birrell (C) 480–481

Dyskinesia: mortality and facial dyskinesia; H. A. McClelland *et al* 310–316

Electrocardiogram: Electrocardiogram changes and therapeutic desipramine and 2-hydroxy-desipramine concentrations in elderly depressives; S. P. Kutcher *et al* 676–679

Electroconvulsive therapy (ECT): Electroconvulsive therapy as a contributor to the production of delusional misidentification; George G. Hay 667–669

Prolactin response induced by ECT and TRH; Yiannis Papakostas *et al* (*Brief report*) 721–723

The Nottingham ECT study: double-blind?; Michael Robinson and Girish Shetty (C) 747

EMBU (*Egna Minnen av Barndoms Uppfestran*) Cross-national invariance of dimensions of parental rearing behaviour: comparison of psychometric data of Swedish depressive and healthy subjects with Dutch target ratings on the EMBU; Willem A. Arrindell *et al* 305–309

Emotion: Expressed emotion and relapse in schizophrenia; J. F. Macmillan *et al* (C) 741–744

Levels of expressed emotion and relapse in depressed patients; Jill M. Hooley *et al* 642–647

Northwick Park study of first episodes of schizophrenia. IV. Expressed emotion and relapse; J. F. Macmillan *et al* 133–143; Julian Leff and Christine Vaughan (C) 215–216

Unpredictability as a correlate of expressed emotion in the relatives of schizophrenics; B. MacCarthy and D. R. Hemsley (*Brief report*) 727–731

Epilepsy: Epilepsy, psychosis, Kraepelin and Bleuler; Cornelia Thiels (C) 107–108

Influence of seizure type and medication on psychiatric symptoms in epileptic patients; S. W. Brown *et al* 300–304

Erickson, Milton: Milton Erickson's contribution to psychiatry; Philip Barker (*Reading about*) 471–475

Erotomania: Erotomania in an Arab; Magda H. El-Badramany and Mohammed A. Aref (C) 106

Erythrocytes, abnormal: Macrocytosis and cognitive decline in Down's syndrome; R. W. Lansdall Welfare and K. E. Hewitt (C) 482–483

Family therapy: Impact of individual and family treatment on the affective climate of families of schizophrenics; Jeri A. Doane *et al* 279–287

Social interventions in the families of schizophrenics; Gwynneth Hemmings (C) 332. Reply; J. Leff *et al* (C) 332–333

Flupenthixol: Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients; J. Esparon *et al* (*Brief report*) 723–725

Fluphenazine: MRC fluphenazine maintenance trial in schizophrenia; Malcolm Peet (C) 482

Folic acid deficiency: Folate deficiency in dementia; M. T. Abou-Saleh *et al* (C) 336–337. Gregory O'Brien and Andrew Clark (C) 337

Folie à deux: Folie à deux in identical twins: interaction of nature and nurture; Arthur Lazarus (*Brief report*) 324–326

Late-onset folie simultanée in a pair of monozygotic twins; Kenneth Kendler *et al* (*Brief report*) 463–465

General practice: Alcoholism and the general practitioner; Alison Mowbray and Neil Kessel 697–700

At risk drinking among general practice attenders: prevalence, characteristics and alcohol-related problems; Michael King 533–540

Depression in general practice; C. V. R. Blacker and A. W. Clare (C) 334. Reply; L. I. Sireling and E. S. Paykel (C) 334–335. T. J. Fahy (C) 746–747

Development of scales to measure treatment attitudes in psychiatry; Greg Wilkinson and Paul Williams 581–586

Germany, West: Adverse drug reactions to first- and second-generation antidepressants: a critical evaluation of drug surveillances data; L. G. Schmidt *et al* 38–43

GHQ-28 (General Health Questionnaire): The validation of the GHQ-28 and the use of the MMSE in neurological in-patients; Keith W. Bridges and David P. Goldberg 548–553

Gilles de la Tourette's syndrome: Asperger's syndrome and Tourette syndrome: the case of the pinball wizard; Jacob Kerbeshian and Larry Burd (*Brief report*) 731–736

Gilles de la Tourette's syndrome in Down's syndrome—a case report; H. Karlinsky *et al* (*Brief report*) 601–604

Gloucester Lunatic Asylum: *A hundred years ago:* Gloucester and the beginnings of the RMPA; Henry Rollin 108

Gluten: A double-blind gluten-free/gluten-load controlled trial in a secure ward population; Dimitrios N. Klissides *et al* 447–452

Guiné-Bissau: A baseline study on mental disorders in Guiné-Bissau; Joop T. V. M. de Jong *et al* 27–32

Hallucinations: True auditory hallucinations as a conversion symptom; Chittaranjan Andrade and Shoba Srinath (*Brief report*) 100–102

Unilateral auditory occlusions and auditory hallucinations; Stephen E. Levick and Eric Peselow (C) 747–748

Haloperidol: Pharmacokinetics and therapeutic efficacy of haloperidol decanoate after loading dose administration; H. De Cuyper *et al* 560–566

Homosexuality: Homosexuality in monozygotic twins reared apart; Elke D. Eckert *et al* 421–425

Hormones: Hormones, mood and sexuality in lactating women; E. M. Alder *et al* 74–79

Hospitalisation: Deficits of chronic schizophrenia in relation to long-term hospitalisation; P. John Mathai and P. S. Gopinath 509–516

Hospitals, general: General hospital psychiatrist: too many tasks and too few roles?; Tom Sensky 151–158

Hospital doctors' management of psychological problems; Richard Mayou and E. B. O. Smith 194–197

Hospitals, psychiatric: Day and full time psychiatric treatment; Ian A. Davidson and Dominic F. Connolly (C) 477. Reply; Peter H. Dick (C) 477–478

The Discovery of the Asylum; David J. Rothman; J. L. T. Birley (*Books reconsidered*) 330–331

Hundred years ago, A: Crighton Royal Institution; Henry Rollin 197

Gloucester and the beginnings of the RMPA; Henry Rollin 108

Lancashire, Rainhill, a murderous assault; Henry Rollin 484

Huntington's chorea: Huntington's chorea without dementia; O. W. J. Quarrell and Peter S. Harper (C) 612–613

Hyperphagia: Depressive symptoms of bulimia nervosa; Peter J. Cooper and Christopher G. Fairburn 268–274

Thirty month follow-up of cognitive-behavioural group therapy for bulimia; Laszlo P. Luka *et al* (C) 614–615

Hyperventilation: Respiratory control in the treatment of panic attacks: replication and extension with concurrent measurement of behaviour and pCO_2; Paul M. Salkovskis *et al* 526–532

Hypothyroidism: Hypothyroidism as a correlate of lateral ventricular enlargement in manic-depressive and neurotic illness; Eve C. Johnstone *et al* 317–321

Hysteria: Conversion without hysteria: a case report and review of the literature; Arieh Shalev and Hanan Munitz 198–203

One hundred cases of hysteria in Eastern Libya: a socio-demographic study; P. Tinnyunt Pu *et al* (*Brief report*) 606–609

Imipramine: Imipramine and amitriptyline plasma concentrations and clinical response in major depression; James H. Kocsis *et al* 52–57

Impotence Cavernosal alpha blockade: a treatment for erectile impotence; Lilian Cameron and Peter Woodruff (C) 107

India: Phobic neuroses in India: a cross-cultural comparison; M. S. Keshavan *et al* (C) 341–342

Information processing: Brain indicators of altered attention and information processing in schizophrenic patients; K. Barrett *et al* 414–420

Informed consent: Mental Health Act and medical treatment without consent; C. J. Thomas (C) 340

Irritable mood: Irritability; Giovanni A. Fava (C) 338–339

Italy: The 'Italian experience' reconsidered; Kathleen Jones and Alison Poletti 144–150

Klinefelter's syndrome: 49, XXXXY chromosome anomaly: an unusual variant of Klinefelter's syndrome; T. Hari Singh and Sudhir Rajkowa (*Brief report*) 209–210

Koro: Koro—a psychophysiological dysfunction?; F. Oyebode *et al* (*Brief report*) 212–214

Korsakoff syndrome: Clinical tests of memory; Michael D. Kopelman 517–525

Kraepelin, E.: Epilepsy, psychosis, Kraepelin and Blueler; Cornelia Thiels (C) 107–108

Kuwait: Erotomania in an Arab; Magda H. El-Badramany and Mohammud A. Aref (C) 106

Lactation: Hormones, mood and sexuality in lactating women; E. M. Alder *et al* 74–79

Language analysis: The diagnosis of schizophrenia by language analysis; William A. Fraser *et al* 275–278

Lectures: *(Eli Lilly 1986)* Mindlessness and brainlessness in psychiatry; Leon Eisenberg 497–508

(19th Blake Marsh, 1985) Socio-psychiatric aspects of the young severely mentally retarded and the family; Annalise Dupont 227–234

Libya: One hundred cases of hysteria in Eastern Libya: a socio-demographic study; Tinnyunt Pu *et al* (*Brief report*) 606–609

Life change events: Early life events and affective disorder revisited; C. Faravelli *et al* 288–295

Parental loss by death in the early childhood of depressed patients and of their healthy siblings; C. Perris *et al* 165–169

Lithium: Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients; J. Esperon *et al* (*Brief report*) 723–725

Lithium and Piroxicam; R. K. Shelley (C) 343

Lithium augmentation in the treatment of delusional depression; M. Pai *et al* (*Brief report*) 736–738

Lithium-induced reaction; Denis P. Eustace (C) 752

Lithium in resistant depression; Samuel I. Cohen and B. A. Johnson (C) 219

Utility of a single-point dosing protocol for predicting steady-state lithium levels; Paul J. Perry *et al* 401–405

London: A comparison of drug-related problems in London Accident and Emergency departments 1975–1982; Hamid Ghodse *et al* 658–662

Lorazepam: Lorazepam dependence and chronic psychosis; A. C. Carr (C) 344

Lymphocytes: Depression, urinary free cortisol excretion and lymphocyte function; Ziad Kronfol *et al* 70–73

Manic depressive psychosis: Hypothyroidism as a correlate of lateral ventricular enlargement in manic-depressive and neurotic illness; Eve C. Johnstone *et al* 317–321

Manic depressive psychosis in a mentally handicapped person—diagnosis and management; S. R. Kadambari (*Brief report*) 595–596

Manic disorder: Hypomania following cognitive therapy; David Kingdon *et al* (*Brief report*) 103–104. A. M. Hughes and J. P. McKane (C) 344

Is mania really incompatible with Down's syndrome?; Iqbal Singh and G. Zolese (C) 613–614

Mania following bereavement: a case report; Stephen J. Rosenman and Helen Tayler (*Brief report*) 468–470

Threatening life events in the onset of schizophrenia, schizophreniform psychosis and hypomania; R. K. Chung *et al* 680–685

Treatment of mania with the cholinomimetic agent RS86; J. C. Krieg and M. Berger (C) 613

Media, The: Schizophrenia and the media; Marjorie Hare (C) 615–616

Memory disorders: Clinical tests of memory; Michael D. Kopelman 517–525

Mental disorders: Baseline study on mental disorders in Guiné-Bissau; Joop T. V. M. de Jong *et al* 27–32

Dexamethasone concentrations and the dexamethasone suppression test in psychiatric disorders; Howard Morris *et al* 66–69

Measurement of social behaviour in psychiatric patients: an assessment of the reliability and validity of the SBS Schedule; Til Wykes and E. Sturt 1–11

Psychiatric disorder, drinking and alcoholism: what are the links? Morris W. Bernadt and Robin M. Murray 393–400

Psychiatric disturbances in the Shy-Drager syndrome; Antonio A. Rizzoli (C) 484

Radio receptor assay of serum neuroleptic levels in psychiatric patients; Janet Krska *et al* 187–193

Self-esteem, vulnerability and psychiatric disorder in the community; J. G. Ingham *et al* 375–385

Mental handicap, *see also* **Mental retardation**

Manic depressive psychosis in a mentally handicapped person—diagnosis and management; S. R. Kadambari (*Brief report*) 595–596

Prevalence of the fragile X syndrome in an institution for the mentally handicapped; David A. Primrose *et al* 655–657

Mental Health Act: Mental Health Act and mental treatment without consent; C. J. Thomas (C) 340

Mental Health (Scotland) Act 1960 Outcome of patients committed to hospital under the Mental Health (Scotland) Act 1960; A. A. McKechnie *et al* 33–37

Mental health services: Psychiatry in the People's Republic of China: William Ll Parry-Jones 638–641

The 'Italian experience' reconsidered: Kathleen Jones and Alison Poletti 144–150

Mental processes: Mindlessness and brainlessness in psychiatry; Leon Eisenberg (*Eli Lilly Lecture 1986*) 497–508

Mental retardation, *see also* **Mental handicap**

49, XXXYY chromosome anomaly in a mentally retarded man; Valerie A. Cowie *et al* (*Brief report*) 210–212

Socio-psychiatric aspects of the young severely mentally retarded and the family; Annalise Dupont (*19th Blake Marsh Lecture, 1985*) 227–234

MHPG (3-methoxy-4-hydroxy-phenylethylene glycol): Should plasma or urinary MHPG be measured in psychiatric research? A critical comment; Johannes G. Filser *et al* (*Comment*) 95–97

Misprint: Misprint of the year: Anna Freud; Andrew C. Smith (C) 344

MMSE (Mini-Mental State Examination): The validation of the GHQ-28 and the use of the MMSE in neurological in-patients; Keith W. Bridges and David P. Goldberg 548–553

Monoamine oxidase inhibitors: Monoamine oxidase inhibitors; Barry Blackwell (C) 216–217
Montgomery-Åsberg Depression Rating Scale: Grade scores of the Montgomery-Åsberg Depression and the Clinical Anxiety scales; R. P. Snaith *et al* (*Brief report*) 599–601
Mood disorders: Hormones, mood and sexuality in lactating women; E. M. Alder *et al* 74–79
MRC: MRC fluphenazine maintenance trial in schizophrenia; Malcolm Peet (C) 482
Munchausen syndrome: Evolution of variants of the Munchausen syndrome; Kenneth Sinanan and Helen Haughton (*Brief report*) 465–467
Mydriatics: Mydriatic response to topical naloxone in opiate abusers; A. H. Ghodse *et al* 44–46

Naloxone: Mydriatic response to topical naloxone in opiate abusers; A. H. Ghodse *et al* 44–46
Neuroleptic malignant syndrome: Neuroleptic malignant syndrome; R. J. Abbott and L. A. Loizau 47–51
Neuroleptic malignant syndrome and lethal catatonia; James Lindesay (C) 342–343
Neuroleptics: Neuroleptics in culture-bound syndromes; Philip E. Harrison-Read (C) 106–107
Radio receptor assay of serum neuroleptic levels in psychiatric patients; Janet Krska *et al* 187–193
Neurotic disorders: Hypothyroidism as a correlate of lateral ventricular enlargement in manic-depressive and neurotic illness; Eve C. Johnstone *et al* 317–321
Relationship between alcoholism and neurosis: evidence from a twin study; M. J. Mullan *et al* 435–441
Nitrous oxide-oxygen: Minimal sedation required with nitrous oxide-oxygen treatment of the alcohol withdrawal state; M. A. Gillman and F. J. Lichtigfeld (*Brief report*) 604–606
Northwick Park: Northwick Park study of first episodes of schizophrenia. I. Presentation of the illness and problems of admission; E. C. Johnstone *et al* 115–120
II. A randomised controlled trial of prophylactic neuroleptic treatment; T. J. Crow *et al* 120–127
III. Short-term outcome in trial entrants and trial eligible patients; J. F. Macmillan *et al* 128–133
IV. Expressed emotion and relapse; J. F. Macmillan *et al* 133–143. Julian Leff and Christine Vaughn (C) 215–216
Nottingham: The Nottingham ECT study: double-blind?; Michael Robinson and Girish Shetty (C) 747
The Nottingham experimental day in psychotherapy: a new approach to teaching psychotherapy to medical students; Mark Aveline and Jane Price 670–675

Obsessive-compulsive disorder: Normal dexamethasone suppression test in obsessive-compulsive disorder; W. Monteiro *et al* (*Brief report*) 326–329
Occupational health services: Occupational mental health—a neglected service; W. E. Mickleburgh 426–434
Opiate dependence: Mydriatic response to tropical naloxone in opiate abusers; A. H. Ghodse *et al* 44–46
Oral habits: Oral habits—a behavioural approach; M. J. P. Ellis (C) 751–752
Organic mental disorders: The validation of the GHQ-28 and the use of the MMSE in neurological in-patients; Keith W. Bridges and David P. Goldberg 548–553
Outcome: Evaluation of a time-limited programme of dynamic group psychotherapy; Barbara M. Dick and Kate Woolff 159–164
Northwick Park study of first episodes of schizophrenia. III. Short-term outcome in trial entrants and trial eligible patients; J. F. MacMillan *et al* 128–133
Outcome of patients committed to hospital under the Mental Health (Scotland) Act 1960; A. A. McKechnie *et al* 33–37
Psycho-social predictors of chronicity in depressed patients; R. M. A. Hirschfeld *et al* 648–654
Schizophrenia with good and poor outcome; V. L. Nimgaonkar and Robin M. Murray (C) 343–344. Tamara Kolakowska (C) 741
Outpatients: What happens when psychiatric out-patients are seen once only?; Linda Gask 663–666

Pain, intractable: Chronic pain syndrome; Gillian Byers *et al* (C) 483–484
Panic: Respiratory control in the treatment of panic attacks: replication and extension with concurrent measurement of behaviour and pCO_2; Paul M. Salkovskis *et al* 526–532
Papaverine: Cavernosal alpha blockade: a treatment for erectile impotence; Lilian Cameron and Peter Woodruff (C) 107
Paranoid disorders: Conversion, paranoia and brain dysfunction; Laurence Miller (C) 481
Parent-child relations: Cross-national invariance of dimensions of parental rearing behaviour: Comparison of psychometric data of Swedish depressives and healthy subjects with Dutch target ratings on the EMBU; Willem A. Arrindell *et al* 305–309
Perceived depriving parental rearing and depression; C. Perris *et al* 170–175
Parietal lobe: A case of parietal lobe atrophy; Paul Dedman and Sharon Numa (*Brief report*) 725–726
Patient drop-outs: Anorexia nervosa: drop-outs from treatment; Maurice Silverman (C) 108
Phentolamine: Cavernosal alpha blockade: a treatment for erectile impotence; Lilian Cameron and Peter Woodruff (C) 107
Phobic disorders: Depression in school phobia; Warren Weinberg *et al* (C) 335. Leslie Atkinson (C) 335–336
Phobic neuroses in India: a cross-cultural comparison; M. S. Keshavan *et al* (C) 341–342
Physician's role: The general hospital psychiatrist: too many tasks and too few roles?; Tom Sensky 151–158
Pinball wizard: Asperger's syndrome and Tourette syndrome: the case of the pinball wizard; Jacob Kerbeshian and Larry Burd (*Brief report*) 731–736
Piroxicam: Lithium and Piroxicam; R. K. Shelley (C) 343
Placebo: Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients; J. Esparon *et al* (*Brief report*) 723–725

Does propranolol have an antipsychotic effect?: A placebo controlled study in acute schizophrenia; Rahul Manchanda and Steven R. Hirsch 701–707

Psychotherapy and placebo; Michael de Mowbray (C) 337–338. H. J. Eysenck (C) 610

Primary health care: Use of SRQ-20 in primary care situations; John Spencer (C) 479–480

Validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of São Paulo; Jair de Jesus Mari and Paul Williams 23–26

Prolactin: Prolactin response induced by ECT and TRH; Yiannis Papakostas *et al* (*Brief report*) 721–723

Propranolol: Criteria for measuring change: statistically significant vs clinically significant; Rahul Manchanda (C) 744–745. Reply; Donald Eccleston and Fuad Hassanyeh (C) 745

Does propranolol have an antipsychotic effect?: A placebo controlled study in acute schizophrenia; Rahul Manchanda and Steven R. Hirsch 701–707

Pseudodementia: Pseudodementia: facts and figures; A. Bulbena and G. E. Berrios 87–94. Brian O'Shea *et al* (C) 611–612

Psychiatric status rating scales: Cross-national invariance of dimensions of parental rearing behaviour: comparison of psychometric data of Swedish depressives and healthy subjects with Dutch target ratings of the EMBU; Willem A. Arrindell *et al* 305–309

Development of scales to measure treatment attitudes in psychiatry; Greg Wilkinson and Paul Williams 581–586

Grade scores of the Montgomery-Åsberg Depression and the Clinical Anxiety scales; R. P. Snaith *et al* (*Brief report*) 599–601

Measurement of social behaviour in psychiatric patients: an assessment of the reliability and validity of the SBS Schedule; Til Wykes and E. Sturt 1–11

Validation of the GHQ-28 and the use of the MMSE in neurological in-patients; Keith W. Bridges and David P. Goldberg 548–553

Validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of São Paulo; Jair de Jesus Mari and Paul Williams 23–26

Psychopharmacology: The AMDP-system in clinical psychopharmacology; D. Bobon and B. Woggon (*Brief report*) 467–468

Psychophysiologic disorders: Hospital doctors' management of psychological problems; Richard Mayou and E. B. O. Smith 194–197

Koro—a psychological dysfunction?; F. Oyebode *et al* (*Brief report*) 212–214

Psychotherapy: Hypomania following cognitive therapy; David Kingdon *et al* (*Brief report*) 103–104. A. M. Hughes and J. P. McKane (C) 344

Nottingham experimental day in psychotherapy: a new approach to teaching psychotherapy to medical students; Mark Aveline and Jane Price 670–675

Psychotherapy and placebo; Michael de Mowbray (C) 337–338. H. J. Eysenck (C) 610

Research on the value of psychotherapy; I. Pilowsky (C) 337

Psychotherapy, brief: Short term intensive psychotherapy—a case history; Richard Gillett (*Brief report*) 98–100

Psychotherapy, group: Dominance hierarchies in psychotherapy groups; James L Kennedy and K. Roy Mackenzie 625–631

Evaluation of a time-limited programme of dynamic psychotherapy; Barbara M. Dick and Kate Wooff 159–164

Thirty month follow-up of cognitive-behavioural group therapy for bulimia; Laszlo P. Luka *et al* (C) 614–615

Psychotic disorders: Epilepsy, psychosis, Kraepelin and Bleuler; Cornelia Thiels (C) 107–108

Lorazepam dependence and chronic psychosis; A. C. Carr (C) 344

Raised plasma cortisol concentrations a feature of drug-free psychotics and not specific for depression; J. E. Christie *et al* 58–65

Puerperal disorders: A multivariate investigation of post-partum mood disturbance; P. R. Gard *et al* 567–575

Radio receptor assay: Radio receptor assay of serum neuroleptic levels in psychiatric patients; Janet Krska *et al* 187–193

Rainhill, Lancashire: A murderous assault: *A hundred years ago;* Henry Rollin 484

Reading about: Milton Erickson's contribution to psychiatry; Philip Barker 471–475

Research: Causal models in psychiatric research; Matthew J. Edlund 713–717

Review articles: Dexamethasone suppression test: fact and artefact; Louise Braddock 363–374

Volatile substance abuse: a review of possible long-term neurological, intellectual and psychiatric sequelae; Maria A. Ron 235–246

RMPA: *A hundred years ago:* Gloucester and the beginnings of the RMPA; Henry Rollin 108

Saudi Arabia: Life events and schizophrenia: a Saudi Arabian study; M. A. F. Al-Khani *et al* 12–22

Schizophrenia: Brain indicators of altered attention and information processing in schizophrenic patients; K. Barrett *et al* 414–420

Criteria for measuring change: statistically significant vs clinically significant; Rahal Manchanda (C) 744–745. Reply; Donald Eccleston and Fuad Hassanyeh (C) 745

Deficits of chronic schizophrenia in relation to long-term hospitalisation; P. John Mathai and P. S. Gopinath 509–516

Depression, hopelessness and suicide in chronic schizophrenia; Robert E. Drake and Paul G. Cotton 554–559

Does propranolol have an antipsychotic effect?: A placebo controlled study in acute schizophrenia; Rahul Manchanda and Steven R. Hirsch 701–707

Double-blind gluten-free/gluten-load controlled trial in a secure ward population; Dimitrios N. Vlissides *et al* 447–452

Effects of intravenous and subcutaneous administration of apomorphine on the clinical symptoms of chronic schizophrenia; E. K. G. Syvälahti *et al* 204–208

Expressed emotion and relapse in schizophrenia; J. F. MacMillan *et al* (C) 741–744

Impact of individual and family treatment on the affective climate of families of schizophrenics; Jeri A. Doane *et al* 279–287

Life events and schizophrenia: a Saudi Arabian study; M. A. F. Al-Khani *et al* 12–22

MRC fluphenazine maintenance trial in schizophrenia; Malcolm Peet (C) 482

Northwick Park study of first episodes of schizophrenia. I. Presentation of the illness and problems relating to admission; E. C. Johnstone *et al* 115–120

II. A randomised controlled trial of prophylactic neuroleptic treatment; T. J. Crow *et al* 120–127

III. Short-term outcome in trial entrants and trial eligible patients; J. F. MacMillan *et al* 128–133

IV. Expressed emotion and relapse; J. F. MacMillan *et al* 133–143. Julian Leff and Christine Vaughn (C) 215–216

Prevalence of schizophrenia in a remote area of Botswana; David I. Ben-Tovim and Josephine N. Cushnie 576–580

Schizophrenia and the media; Marjorie Hare (C) 615–616

Schizophrenia with good and poor outcome; V. L. Nimgaonkar and Robin M. Murray (C) 343–344. Tamara Kolakowska (C) 741

Schizophrenia and ethnicity; S. P. Sashidharan and M. Lipsedge (C) 484

Social interventions in the families of schizophrenics; Gwynneth Hemmings (C) 332. Reply; J. Leff *et al* (C) 332–333

Threatening life events in the onset of schizophrenia, schizophreniform psychosis and hypomania; R. K. Chung *et al* 680–685

Unilateral auditory occlusions and auditory hallucinations; Stephen E Levick and Eric Peselow (C) 747–748

Unpredictability as a correlate of expressed emotion in the relations of schizophrenics; B. MacCarthy *et al* (*Brief report*) 727–731

Schizophrenia, paranoid: Erotomania in an Arab; Magda H. El-Badramany and Mohammed A. Aref (C) 106

'Schizophrenia, sluggish': Political hazards in the diagnosis of 'sluggish schizophrenia'; Harold Merskey and Bronislava Shafran 247–256

Schizophrenic psychology: The diagnosis of schizophrenia by language analysis; William I. Fraser *et al* 275–278

Schizophreniform psychosis: Threatening life events in the onset of schizophrenia, schizophreniform psychosis and hypomania; R. K. Chung *et al* 680–685

Schneider, K.: Schneiderian first rank symptoms caused by benzodiazepine withdrawal; Keith Roberts and Neil Vass (*Brief report*) 593–594

Scotland: Outcome of patients committed to hospital under the Mental Health (Scotland) Act 1960; A. A. McKechnie *et al* 33–37

Seasons: Seasonal affective disorder; J. R. King (C) 478. Reply; Norman E. Rosenthal and Steven P. James (C) 478–479

Seasonal variation in suicides for males and females; David Lester (C) 219

Self assessment (psychology): Self-esteem, vulnerability and psychiatric disorder in the community; J. G. Ingham *et al* 375–385

Self-poisoning: Blood alcohol survey in patients with self-poisoning; R. Varadaraj and J. D. Mendonca (C) 615

Ethnic differences in self-poisoning: a comparison of Asian and White groups; John Merrill and John Owens 708–712

Social determinants of self-poisoning; Maura Daly *et al* 406–413

Sex behaviour: Does viloxazine really improve sex drive?; A double-blind controlled study; Diego de Leo and Guido Magni (*Brief report*) 597–599

Hormones, mood and sexuality in lactating women; E. M. Alder *et al* 74–79

Shared paranoid disorder: Folie à deux in identical twins: interaction of nature and nurture; Arthur Lazarus (*Brief report*) 324–326

Late-onset folie simultanée in a pair of monozygotic twins; Kenneth Kendler *et al* (*Brief report*) 463–465

Shy-Drager syndrome: Psychiatric disturbances in the Shy-Drager syndrome; Antonio A. Rizzoli (C) 484

Sick role: The evaluation of illness behaviour and exaggeration of disability, J. R. Clayer *et al* 296–299

Sleep: Awake, perchance asleep?; S. E. Southmayd *et al* (C) 748–749

Locus of control in short and long sleepers; Anand Kumar and A. K. Vaidya (*Brief report*) 739–740

Sneezing: Complaints of inability to sneeze; Andrew Clark (C) 218–219

Social behaviour disorders: The measurement of social behaviour in psychiatric patients: an assessment of the reliability and validity of the SBS Schedule; Til Wykes and E. Sturt 1–11

Social environment: Social determinants of self-poisoning; Maura Daly *et al* 406–413

Socio-environmental therapy: Socio-psychiatric aspects of the young severely mentally retarded and the family; Annalise Dupont (*19th Blake Marsh Lecture, 1985*) 227–234

Somnambulism: On serious violence during sleep-walking; Michael J. Tarsh (C) 476: A. A. Bartholomew (C) 476–477

Spiropiperidyl derivative RS86: Treatment of mania with the cholinomimetic agent RS86; J. C. Krieg and M. Berger (C) 613

SRQ-20 (Self-Report Questionnaire-20 items)

Use of SRQ-20 in primary care situations; John Spencer (C) 479–480

Validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of São Paulo; Jair de Jesus Mari and Paul Williams 23–26

Stress, psychological: Epidemiology of life events and long-term difficulties, with some reflections on the concept of independence; P. McC. Miller *et al* 686–696

Life events and schizophrenia: a Saudi Arabian study; M. A. F. Al-Khani *et al* 12–22

Women, life events and drinking problems; Carole A. Allan and D. Cooke (*Comment*) 462

Substance abuse: Volatile substance abuse: a review of possible long-term neurological, intellectual and psychiatric sequelae; Maria A. Ron (*Review article*) 235–246

Substance withdrawal syndrome: Minimal sedation required with nitrous oxide-oxygen treatment of the alcohol withdrawal state; M. A. Gillman and F. J. Lichtigfeld (*Brief report*) 604–606

Suicide: Depression, hopelessness and suicide in chronic schizophrenia; Robert E. Drake and Paul G. Cotton 554–559

Seasonal variation in suicides for males and females; David Lester (C) 219

Suicide, attempted: Blood alcohol survey in patients with self-poisoning; R. Karadaraj and J. D. Mendonca (C) 615

Ethnic differences in self-poisoning: a comparison of Asian and White groups; John Merrill and John Owens 708–712

Social determinants of self-poisoning; Maura Daly *et al* 406–413

Symptoms and general pathology: Positive and negative symptoms in psychiatry; Michael R. Trimble (*Comment*) 587–589

Toluene: Volatile substance abuse: a review of possible long-term neurological, intellectual and psychiatric sequelae; Maria A. Ron (*Review article*) 235–246

Teaching: The Nottingham experimental day in psychotherapy: a new approach to teaching psychotherapy to medical students; Mark Aveline and Jane Price 670–675

Thioridazine: Criteria for measuring change: statistically significant vs clinically significant; Rahul Manchanda (C) 744–745. Reply; Donald Eccleston and Fuad Hassanyeh (C) 745

Tomography, X-ray computed: Computed tomography in the elderly: change over time in a normal population; Jonathan M. Bird *et al* 80–85

TRH, thyrotropin-releasing hormone: Prolactin response induced by ECT and TRH; Yiannis Papakostas *et al* (*Brief report*) 721–723

Tryptophan: A multivariate investigation of post-partum mood disturbance; P. R. Gard *et al* 567–575

Twins, *see* **Diseases in twins**

USSR: Political hazards in the diagnosis of 'sluggish schizophrenia'; Harold Merskey and Bronislava Shafran 247–256

Viloxazine: Does viloxazine really improve sex drive?: A double-blind controlled study; Diego De Leo and Guido Magni (*Brief report*) 597–599

Violence: On serious violence during sleep-walking; Michael J. Tarsh (C) 476. A. H. Bartholomew (C) 476–477

PART II—CONTRIBUTORS

Abbott, R. J. and Loizou, L. A. Neuroleptic malignant syndrome 47

Abou-Saleh, M. T., Spalding, E. and Kellett, J. (C) Folate deficiency in dementia 336

Agras, W. Stewart (C) *See* Luka, Laszlo P.

Ah-Sing, Eric (C) *See* Watkins, Soral E.

Alder, E. M., Cook, A., Davidson, D., West, C. and Bancroft, J. Hormones, mood and sexuality in lactating women 74

Alexander, Bruce *See* Perry, Paul J.

Al-Khani, M. A. F., Bebbington, P. E., Watson, J. P. and House, F. Life events and schizophrenia: A Saudi Arabian study 12

Allan, Carole A. and Cooke, D. Women, life events and drinking problems (*Comment*) 462

Al-Samarrai, Mohammad *See* Ghodse, Hamid

Ambonetti, A. *See* Faravelli, C.

Andrade, Chittaranjan and Srinath, Shoba True auditory hallucinations as a conversion symptom (*Brief report*) 100

Andreasen, Nancy C. *See* Young, Michael A.

——*See* Hirschfeld, R. M. A.

Aref, Mohammed, A. *See* El-Badramany, Magda H.

Arrindell, Willem A., Perris, Carlo, Perris, Hjördis, Eisemann, Martin, Van der Ende, Jan and Von Knorring, Lars Cross-national invariance of dimensions of parental rearing behaviour: comparison of psychometric data of Swedish depressives and healthy subjects with Dutch target ratings on the EMBU 305

——*See* Perris, C.

Atkinson, Leslie (C) Depression in school phobia 335

Aveline, Mark and Price, Jane The Nottingham experimental day in psychotherapy: a new approach to teaching psychotherapy to medical students 670

Bancroft, J. *See* Alder E. M.

Barrett, K., McCallum, W. C. and Pocock, P. V. Brain indicators of altered attention and information processing in schizophrenic patients 414

Bartholomew, A. A. (C) On serious violence during sleep-walking 477

Bartlett, J. R. *See* Standish-Barry, H. M. A. S.

Bebbington, Paul (C) Depression: distress or disease? 479

Bebbington, P. E. *See* Al-Khani, M. A. F.

Beckmann, Helmut *See* Filser, Johannes G.

Ben-Tovim, David I. and Cushnie, Josephine The prevalence of schizophrenia in a remote area of Botswana 576

Berg, J. M. *See* Karlinsky, H.

Berger, M. (C) *See* Krieg, J. C.

Berkowitz, R. (C) *See* Leff, J.

Bernadt, Morris W. and Murray, Robin M. Psychiatric disorder, drinking and alcoholism: what are the links? 393

Berrios, G. E. *See* Bulbena, A.

Bewley, T. H. *See* Ghodse, A. H.

——*See* Ghodse, Hamid

Bird, Jonathan H., Levy, Raymond and Jacoby, Robin J. Computed tomography in the elderly: changes over time in a normal population 80

Birley, J. L. T. *Books reconsidered:* David J. Rothman's *The Discovery of the Asylum* 330

Birrell, Peter (C) *See* Christensen, Helen

Birtchnell, John (C) Anniversary Reactions 610

Blackburn, I. M. *See* Christie, J. E.

Blacker, C. V. R. and Clare, A. W. (C) Depression in general practice 333

Blackwell, Barry (C) Monoamine oxidase inhibitors 216
Blackwood, D. H. R. *See* Christie, J. E.
Bleich, A., Garb, R. and Kottler, M. Treatment of prolonged combat reaction (*Annotation*) 493
Bobon, D. and Woggon, B. The AMDP-system in clinical psychopharmacology (*Brief report*) 467
Bohlen, Joseph *See* Eckert, Elke D.
Bolla-Wilson, Karen *See* Robinson, Robert G.
Bollen, J. *See* De Cuyper, H.
Bookless-Pratz, C. L. *See* Clayer, J. R.
Bouchard, Thomas J. *See* Eckert, Elke D.
Bouras, N. *See* Standish-Barry, H. M. A. S.
Bowden, Charles *See* Kocsis, James H.
Boyd, Elizabeth *See* Primrose, David A.
Braddock, Louise The dexamethasone suppression test: fact and artefact (*Review article*) 363
Bridges, Keith W. and Goldberg, David P. The validation of the GHQ-28 and the use of the MMSE in neurological in-patients 549
Bridges, P. K. *See* Standish-Barry, H. M. A. S.
Brown, S. W., McGowan, M. E. L. and Reynolds, E. H. The influence of seizure type and medication on psychiatric symptoms in epileptic patients 300
Brunet, D. G. (C) *See* Southmayd, S. E.
Brunswick, David *See* Kocsis, James H.
Bulbena, A. and Berrios, G. E. Pseudodementia: facts and figures 87
Burd, Larry *See* Kerbeshian, Jacob
Byers, Gillian, Cullen, John and O'Boyle, Ciarán (C) Chronic pain syndrome 483

Cairns, J. (C) *See* Southmayd, S. E.
Calloway, S. P. and Dolan, R. J. (C) Depression and urinary free cortisol 611
Cameron, Lillian and Woodruff, Peter (C) Cavernosal alpha blockade: A treatment for erectile impotence 107
Carr, A. C. (C) Lorazepam dependence and chronic psychosis 344
Carr, Vaughan *See* Morris, Howard
Caroll, Bernard J. (C) Depression and urinary free cortisol 218
——*See* Kronfol, Ziad
Chambers, J. (C) *See* Keshavan, M. S.
Checkley, S. *See* Monteiro, W.
Chiba, Shigeru, Takahashi, Saburo and Miyagishi, Tsutomu (C) Psychiatric manifestation as an early symptom of Behçet's disease 753
Christensen, Helen and Birrell, Peter (C) Diagnostic criteria for dementia in DSM-III 481
Christie, J. E., Whalley, L. J., Dick, H., Blackwood, D. H. R., Blackburn, I. M. and Fink, G. Raised plasma cortisol concentrations are a feature of drug-free psychotics and are not specific for depression 58
Chung, R. K., Langeluddecke, P. and Tennant, C. Threatening life events in the onset of schizophrenia, schizophreniform psychosis and hypomania 680
Clare, A. W. (C) *See* Blacker, C. V. R.
Clark, Andrew (C) Complaints of inability to sneeze 218
——, (C) *See* O'Brien, Gregory
Clark, David M. *See* Salkovskis, Paul M.
Clayer, J. R., Bookless-Pratz, C. L. and Ross, M. W. The evaluation of illness behaviour and exaggeration of disability 296
Clayton, P. J. *See* Hirschfeld, R. M. A.
Clifford, Michael A. (C) *See* Watkins, Sarah E.
Cohen, Samuel I. and Johnson, B. A. (C) Lithium in resistant depression 219
Colter, N. *See* Johnstone, Eve C.
Connolly, Dominic F. (C) *See* Davidson, Ian A.
Conte, G. *See* Faravelli, C.
Conway, Miranda *See* Daly, Maura
Cook, A. *See* Alder, E. M.
Cooke, D. *See* Allan, Carole A.
Cooper, Peter J. and Fairburn, Christopher G. The depressive symptoms of bulimia nervosa 268
Corser, A. *See* McKechnie, A. A.
Cotton, Paul G. *See* Drake, Robert E.
Cowie, Valerie A., Singh, Rameshwarie K. and Wheater, Richard 49 XXXYY chromosome anomaly in a mentally retarded man (*Brief report*) 210
—— (C) *See* Watkins, Sarah E.
Crawford, E. *See* Karlinsky, H.
Crow, T. J., MacMillan, J. F., Johnson, A. L. and Johnstone, E. C. The Northwick Park Study of first episodes of schizophrenia: II. A randomised controlled trial of prophylactic neuroleptic treatment 120
——, *See* Johnstone, E. C.
——, *See* MacMillan, J. F.
——, *See* MacMillan, J. F.
——, (C) *See* MacMillan, J. F.
Cullen, John (C) *See* Byers, Gillian
Cushnie, Josephine *See* Ben-Tovim, David I.

Daly, Maura, Conway, Miranda and Kelleher, Michael J. Social determinants of self-poisoning 406
Davidson, D. *See* Alder, E. M.
Davidson, Ian A. and Connolly, Dominic F. (C) Day and fulltime psychiatric treatment 477
Davidson, Jonathan and Turnbull, Craig D. Diagnostic significance of vegetative symptoms in depression 442
Davison, K. *See* Oyebode, F.
Dean, C. *See* Surtees, P. G.
——*See* McC. Miller, P.
Deane, A. G. *See* Pai, M.
De Cuyper, H., Bollen, J., Van Praag, M. M. and Verstraeten, D. Pharmacokinetics and therapeutic efficacy of haloperidol decanoate after loading dose administration 560
Dedman, Paul and Numa, Sharon A case of parietal lobe atrophy (*Brief report*) 725
de Jong, Joop T. V. M., de Klein, Guus A. J. and ten Horn, Sineke G. H. M. M. A baseline study on mental disorders in Guiné-Bissau 27
de Klein, Guus A. J. *See* de Jong, Joop, T. V. M.
De Leo, Diego and Magni, Guido Does viloxazine really improve sex drive? A double-blind controlled study (*Brief report*) 597
de Leon Molina, J., Muñoz Ruata, J. and Pico Soler, E. (C) Is there a right-hemisphere dysfunction in Åsperger's syndrome? 746

Delva, N. J. (C) *See* Southmayd, S. E.
de Mowbray, Michael (C) Psychotherapy and placebo 337
Dick, Barbara M. and Wooff, Kate An evaluation of a time-limited programme of dynamic group psychotherapy 159
Dick, H. *See* Christie, J. E.
Dick, Peter H. (C) Day and fulltime psychiatric treatment 478
Dickerson, John W. T. (C) *See* Watkins, Sarah E.
Doane, Jeri A., Goldstein, Michael J., Miklowitz, David J. and Falloon, Ian R. H. The impact of individual and family treatment on the affective climate of families of schizophrenics 279
Dolan, R. J. (C) *See* Calloway, S. P.
Drake, Robert E. and Cotton, Paul G. Depression, hopelessness and suicide in chronic schizophrenia 555
Dubbin, J. D. *See* Kutcher, S. P.
Dunner, Frederick J. *See* Perry, Paul J.
Dupont, Annalise Socio-psychiatric aspects of the young severely mentally retarded and the family (*Lecture*) 227
Dutta, D. *See* McClelland, H. A.

Eccleston, Donald and Hassanyeh, Fuad (C) Criteria for measuring change: statistical significance vs clinical significance 745
Eckert, Elke D., Bouchard, Thomas J., Bohlen, Joseph and Heston, Leonard L. Homosexuality in monozygotic twins reared apart 421
Edlund, Matthew J. Causal models in psychiatric research (*Comment*) 713
Edwards, Griffith *See* Ghodse, Hamid
Eisemann, Martin *See* Arrindell, Willem A.
——*See* Perris, C.
Eisenberg, Leon Mindlessness and brainlessness in psychiatry (*Lecture*) 497
El-Badramany, Magda H. and Aref, Mohammed, A. (C) Erotomania in an Arab 106
Ellis, M. P. J. (C) Oral habits—a behavioural approach 752
El-Roey, Ali M. *See* Pu, Tinnyunt
Emslie, Graham (C) *See* Weinberg, Warren
Esparon, J., Kolloori, J., Naylor, G. J., McHarg, A. M., Smith, A. H. W. and Hopwood, S. E. Comparison of the prophylactic action of Flupenthixol with placebo in lithium treated manic depressive patients (*Brief report*) 723
Eustace, Denis P. (C) Lithium-induced reaction 752
Eysenck, H. J. (C) Psychotherapy and placebo 610

Fahy, T. J. (C) Depression in general practice 747
Fairburn, Christopher G. *See* Cooper, Peter J.
Falloon, Ian R. H. *See* Doane, Jeri A.
Faravelli, C., Sacchetti, E., Ambonetti, A., Conte, G., Pallanti, S. and Vita, A. Early life events and affective disorder revisited 288
Farr, Pat *See* Kingdon, David
Fava, Giovani A. (C) Irritability 338
Fichter, Manfred M., Meister, Irmgard and Koch, Hans-Joachim The measurement of body image disturbances in anorexia nervosa: experimental comparison of different methods 453
Filser, Johannes G., Müller, Walter E. and Beckmann, Helmut Should plasma or urinary MHPG be measured in psychiatric research? A critical comment (*Comment*) 95
Fine, Eric W. (C) Chromosome anomaly 753
Fink, G. *See* Christie, J. E.
Fraser, William I., King, Kathleen M., Thomas, Philip and Kendell, Robert E. The diagnosis of schizophrenia by language analysis 275
Freeman, H. L. *See* Lodge, G. J.

Garb, R. *See* Bleich, A.
Gard, P. R., Handley, S. L., Parsons, A. D. and Waldron, G. A multivariate investigation of post-partum mood disturbance 567
Gask, Linda What happens when psychiatric out-patients are seen once only? 663
Ghodse, A. H., Bewley, T. H., Kearney, M. K. and Smith, S. E. Mydriatic response to topical naloxone in opiate abusers 44
——**, Stapleton, John, Edwards, Griffith, Bewley, Thomas and Al-Samarrai, Muhammad.** A comparison of drug-related problems in London accident and emergency departments 1975–1982 658
Gillett, Richard Short-term intensive psychotherapy —a case history (*Brief report*) 98
Gilliland, Judy *See* Morris, Howard
Gillman, M. A. and Lichtigfeld, F. J. Minimal sedation required with nitrous oxide—oxygen treatment of the alcohol withdrawal state (*Brief report*) 604
Girish, Shetty (C) *See* Robinson, Michael
Gold, A. *See* MacMillan, J. F.
—— (C) *See* Macmillan, J. F.
Goldberg, David P. *See* Bridges, Keith W.
Goldstein, Michael J. *See* Doane, Jeri A.
Gopinath, P. S. *See* John Mathai, P.
Gosden, Christine *See* Primrose, David A.
Greden, John *See* Kronfol, Ziad
Grohmann, R. *See* Schmidt, L. G.
Gurling, H. M. D. *See* Mullan, M. J.

Hale, A. S. *See* Standish-Barry, H. M. A. S.
Handley, S. L. *See* Gard, P. R.
Hanin, Israel *See* Kocsis, James H.
Hare, Marjorie (C) Schizophrenia and the media 615
Harper, Peter S. (C) *See* Quarrell, O. W. J.
Harris, Brian, Young, John and Hughes, Bill Comparative effects of seven antidepressant regimes on appetite, weight and carbohydrate preference (*Brief report*) 590
Harrison-Read, Philip E. (C) Neuroleptics in culture-bound syndromes 106
Harrop, F. M. *See* Snaith, R. P.
Hassanyeh, Fuad (C) *See* Eccleston, Donald
Haughton, Helen *See* Sinanan, Kenneth
Hay, George G. Electroconvulsive therapy as a contributor to the production of delusional misidentification 667
Hemmings, Gwynneth (C) Social interventions in the families of schizophrenics 332

Hemsley, David *See* MacCarthy, Brigid
Heston, Leonard L. *See* Eckert, Elke D.
Hewitt, K. E. (C) *See* Lansdall Welfare, R. W.
Hietala, J. *See* Sylvalähti, E. K. G.
Hirsch, Steven R. *See* Manchanda, Rahul
Hirschfeld, Robert M. A. *See* Young, Michael A.
——**, Klerman, G. L., Andreasen, N. C., Clayton, P. J. and Keller, M. B.** Psycho-social predictors of chronicity in depressed patients 648
Holmgren, S. *See* Perris, C.
Hooley, Jill M., Orley, John and Teasdale, John D. Levels of expressed emotion and relapse in depressed patients 642
Hooper, Michael *See* Morris, Howard
Hopwood, S. E. *See* Esparon, J.
House, F. *See* Al-Khani M. A. F.
House, J. Daniel *See* Kronfol, Ziad
Hughes, A. M. and McKane, J. P. (C) Hypomania following cognitive therapy 344
Hughes, Bill *See* Harris, Brian

Imam, Kareema *See* Pu, Tinnyunt
Ingham, J. G., Kreitman, N. B., McC. Miller, P. Sashidharan, S. P. and Surtees, P. G. Self-esteem, vulnerability and psychiatric disorder in the community 375
——*See* McC. Miller, P.

Jacoby, Robin J. *See* Bird, Jonathan M.
Jagoe, R. *See* Johnstone, Eve C.
Jain, J. *See* Renvoize, E. B.
James, Steven P. (C) *See* Rosenthal, Norman E.
Jamieson, R. *See* Oyebode, F.
Jenner, F. A. *See* Vlissides, Dimitrios N.
Jerome, Laurence (C) Capgras syndrome 751
Johnson, A. L. *See* Crow, T. J.
——, *See* Johnstone, E. C.
——, *See* MacMillan, J. F.
——, *See* MacMillan, J. F.
——, (C) *See* MacMillan, J. F.
Johnson, B. A. (C) *See* Cohen, Samuel I.
Johnstone, E. C., Crow, T. J., Johnson, A. L. and MacMillan, J. F. The Northwick Park study of first episodes of schizophrenia. I Presentation of the illness and problems relating to admission 115
——**, Owens, D. G. C., Crow, T. J., Colter N., Lawton, Claire A., Jagoe, R. and Kreel, L.** Hypothyroidism as a correlate of lateral ventricular enlargement in manic-depressive and neurotic illness 314
——*See* Crow, T. J.
——*See* MacMillan, J. F.
——, *See* MacMillan, J. F.
——, (C) *See* MacMillan, J. F.
Jones, David R. O. *See* Salkovskis, Paul M.
Jones, Kathleen and Poletti, Alison The 'Italian experience' reconsidered 144
Joseph, Anthony, B. (C) Capgras syndrome 750

Kadambari, S. R. Manic depressive psychosis in a mentally handicapped person—diagnosis and management (*Brief report*) 595
Kaplan, Edith *See* Robinson, Robert G.
Karlinsky, H., Berg, J. M., Moldofsky, H. and Crawford, E. Gilles de la Tourette's syndrome in Down's syndrome—a case report (*Brief report*) 601
Katz, Randy *See* MacCarthy, Brigid
Kearney, M. K. *See* Ghodse, A. H.
Kelleher, Michael J. *See* Daly, Maura
Keller, M. B. *See* Hirschfeld, R. M. A.
Kellett, J. (C) *See* Abou-Saleh, M. T.
Kendell, Robert E. *See* Fraser, William I.
Kendler, Kenneth S., Robinson, Gillian, McGuire, Mary and Spellman, Mary P. Late-onset folie simultanée in a pair of monozygotic twins (*Brief report*) 463
Kennedy, James L. and MacKenzie, K. Roy Dominance hierarchies in psychotherapy groups (*Annotation*) 625
Kerbeshian, Jacob and Burd, Larry Asperger's syndrome and Tourette syndrome: the case of the pinball wizard (*Brief report*) 731
Kerr, T. A. *See* McClelland, H. A.
Keshavan, M. S., Yeragani, V. K. and Chambers, J. Phobic neuroses in India: a cross-cultural comparison 341
Kessel, Neil *See* Mowbray, Alison
King, J. R. (C) Seasonal affective disorder 478
King, Kathleen, M. *See* Fraser, William I.
King, Michael At risk drinking among general practice attenders: prevalence, characteristics and alcohol—related problems 533
Kingdon, David, Farr, Pat, Murphy, Siobhan and Tyrer, Peter Hypomania following cognitive therapy (*Brief report*) 103
Klerman, Gerald L. *See* Young, Michael A.
——*See* Hirschfeld, R. M. A.
Koch, Hans-Joachim *See* Fichter, Manfred M.
Kocsis, James H., Hanin, Israel, Bowden, Charles and Brunswick, David Imipramine and amitriptyline plasma concentrations and clinical response in major depression 52
Kolakowska, Tamara (C) Schizophrenia with good and poor outcome 741
Kolloori, J. *See* Esparon, J.
Kopelman, Michael D. Clinical tests of memory 517
Kottler, M. *See* Bleich, A.
Kreel, L. *See* Johnstone, Eve C.
Kreitman, N. B. *See* Ingham, J. G.
——*See* McC. Miller, P.
Krieg, J. C. and Berger, M. (C) Treatment of mania with cholinomimetic agent RS 86 613
Kronfol, Ziad, House, J. Daniel, Silva, Joseph Jr., Greden, John and Carroll, Bernard J. Depression, urinary free cortisol excretion and lymphocyte function 70
Krska, Janet, Sampath, G., Shah, A. and Soni, S. D. Radio receptor assay of serum neuroleptic levels in psychiatric patients 187
Kuipers, L. (C) *See* Leff, J.
——*See* MacCarthy, Brigid
Kumar, Anand and Vaidya, A. K. Locus of control in short and long sleepers (*Brief report*) 739
Kutcher, S. P., Reid, K., Dubbin, J. D. and Shulman, K. I. Electrocardiogram changes and therapeutic Desipramine and 2-hydroxy-desipramine concentrations in elderly depressives 676

Langeluddecke, P. *See* Chung, R. K.

Lansdall Welfare, R. W. and Hewitt, K. E. (C) Macrocytosis and cognitive decline in Down's syndrome 483

Lawton, Claire A. *See* Johnstone, Eve C.

Lazarus, Arthur Folie à deux in identical twins: interaction of nature and nurture (*Brief report*) 324

Leff, J., Berkowitz, R., Kuipers, L. and Sturgeon, D. (C) Social interventions in the families of schizophrenics 332

——, **and Vaughn, Christine** (C) First episodes of schizophrenia 215

Lester, David (C) Seasonal variation in suicides for males and females 219

Letemendia, F. J. J. (C) *See* Southmayd, S. E.

Levick, Stephen E. and Peselow, Eric (C) Unilateral auditory occlusions and auditory hallucinations 748

Levy, Raymond *See* Bird, Jonathan H.

Lichtigfeld, F. J. *See* Gillman, M. A.

Lindesay, James (C) Neuroleptic malignant syndrome and lethal catatonia 342

Lipsey, John R. *See* Robinson, Robert G.

Littlewood, Roland (C) Transcultural psychiatry 340

Lodge, G. J. and Freeman, H. L. Clovoxamine and Doxepin in major depressive disorder: a double-blind controlled trial (*Brief report*) 718

Loizou, L. A. *See* Abbott, R. J.

Luka, Laszlo P., Agras, W. Stewart and Schneider, John A. (C) Thirty month follow-up of cognitive-behavioural group therapy for bulimia 614

McCallum, W. C. *See* Barrett, K.

MacCarthy, Brigid, Hemsley, David, Schrank-Fernandez, Candy, Kuipers, Liz and Katz, Randy Unpredictability as a correlate of expressed emotion in the relatives of schizophrenics (*Brief report*) 727

McClelland, A. A., Dutta, D., Metcalfe, A. and Kerr, T. A. Mortality and facial dyskinesia 310

McCollam, Catherine (C) *See* O'Shea, Brian

McGowan, M. E. L. *See* Brown, S. W.

McGuire, Mary *See* Kendler, Kenneth S.

McHarg, A. M. *See* Esparon, J.

McKane, J. P. (C) *See* Hughes, A. M.

McKechnie, A. A., Corser, A. and McMillan, V. R. Outcome of patients committed to hospital under the Mental Health (Scotland) Act 1960 33

MacKenzie, K. Roy *See* Kennedy, James L.

MacMillan, J. F., Crow, T. J., Johnson, A. L. and Johnstone, E. C. The Northwick Park study of first episodes of schizophrenia: III. Short-term outcome in trial entrants and trial eligible patients 128

——, **Gold, A., Crow, T. J., Johnson, A. L. and Johnstone, E. C.** The Northwick Park study of first episodes of schizophrenia: IV Expressed emotion and relapse 133

——, *See* Crow, T. J.

——, *See* Johnstone, E. C.

——, (C) **Gold, A., Crow, T. J., Johnson, A. L. and Johnstone, E. C.** Expressed emotion and relapse in schizophrenia 743

McMillan, V. R. *See* McKechnie, A. A.

McC. Miller, P. *See* Ingham, J. G.

——, **Dean, C., Ingham, J. G., Kreitman, N. B., Sashidharan, S. P. and Surtees, P. G.** The epidemiology of life events and long-term difficulties, with some reflections on the concept of independence 686

Magni, Guida *See* De Leo, Diego

Manchanda, Rahul and Hirsch, Steven R. Does propranolol have an antipsychotic effect? A placebo controlled study in acute schizophrenia 701

—— (C) Criteria for measuring change: statistical significance vs clinical significance 745

Markianos, Manolis *See* Papakostas, Yiannis

Mari, Jair de Jesus and Williams, Paul A validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of São Paulo 23

Marks, I. M. *See* Monteiro, W.

Mathai, P. John and Gopinath, P. S. Deficits of chronic schizophrenia in relation to long-term hospitalisation 509.

Matmati, Rabia *See* Primrose, David A.

Mayou Richard and Smith, E. B. O. Hospital doctors' management of psychological problems 194

Meister, Irmgard *See* Fichter, Manfred M.

Mendonca, J. D. (C) *See* Varadaraj, R.

Merrill, John and Owens, John Ethnic differences in self-poisoning: a comparison of Asian and White groups 708

Merskey, Harold and Shafran, Bronislava Political hazards in the diagnosis of 'sluggish schizophrenia' 247

Metcalfe, A. *See* McClelland, H. A.

Mickleburgh, W. E. Occupational mental health—a neglected service 426

Miklowitz, David J. *See* Doane, Jeri A.

Miller, Laurence (C) Conversion, paranoia and brain dysfunction 481

Mohamed, E. *See* Pu, Tinnyunt

Moldofsky, H. *See* Karlinsky, H.

Monteiro, W., Marks, I. M., Noshirvani, H. and Checkley, S. Normal dexamethasone suppression test in obsessive-compulsive disorder (*Brief report*) 326

Morris, Howard, Carr, Vaughan, Gilliland, Judy and Hooper, Michael Dexamethasone concentrations and the dexamethasone suppression test in psychiatric disorders 66

Mowbray, Alison and Kessel, Neil Alcoholism and the general practitioner 697

Mullan, M. J., Gurling, H. M. D., Oppenheim, B. E. and Murray, R. M. The relationship between alcoholism and neurosis: evidence from a twin study 435

Mullaney, J. *See* Oyebode, F.

Müller, Walter E *See* Filser, Johannes G.

Müller-Oerlinghausen, B. *See* Schmidt, L. G.

Munitz, Hanan *See* Shalev, Arieh

Muñoz Ruata, J. (C) *See* de Leon Molina, J.

Murphy, Siobhan *See* Kingdon, David

Murray, R. M. *See* Mullan, M. J.

Murray, Robin M. *See* Bernadt, Morris W.

—— (C) *See* Nimgaonkar, V. L.

Naylor, G. J. *See* Esparon, J.

Newby, D. A. *See* Snaith, R. P.

Newton, Marjorie *See* Primrose, David A.
Nimgaonkar, V. L. and Murray, Robin M. (C) Schizophrenia with good and poor outcome 343
Noshirvani, H. *See* Monteiro, W.
Numa, Sharon *See* Dedman, Paul

O'Boyle, Ciarán (C) *See* Byers, Gillian
O'Brien, Gregory and Clark, Andrew (C) Folate deficiency in dementia 337
Ochsenfahrt, H. *See* Schmidt, L. G.
Oppenheim, B. E. *See* Mullan, M. J.
Orley, John *See* Hooley, Jill M.
O'Shea, Brian, Rahill, Martin and McCollam, Catherine (C) Pseudodementia: facts and figures 611
Owens, D. G. C. *See* Johnstone, Eve C.
Owens, John *See* Merrill, John
Oyebode, F., Jamieson, R., Mullaney, J. and Davison, K. Koro—A psychophysiological dysfunction? (*Brief report*) 212

Pai, M., White, A. C. and Deane, A. G. Lithium augmentation in the treatment of delusional depression (*Brief report*) 736
Pallanti, S. *See* Faravelli, C.
Papadimitriou, George *See* Papakostas, Yiannis
Papakostas, Yiannis, Markianos, Manolis, Papadimitriou, George and Stefanis, Costos Prolactin response induced by ECT and TRH (*Brief report*) 721
Parry-Jones, William Ll. Psychiatry in the People's Republic of China 632
Parsons, A. D. *See* Gard, P. R.
Paykel, E. S. (C) *See* Sireling, L. I.
Peet, Malcolm (C) MRC fluphenazine maintenance trial in schizophrenia 482
Perris, C., Holmgren, S., von Knorring, L. and Perris, H. Parental loss by death in the early childhood of depressed patients and of their healthy siblings 165
Perris, C., Arrindell, W. A., Perris, H., Eisemann, M., van der Ende, J. and von Knorring, L. Perceived depriving parental rearing and depression 170
——*See* Arrindell, Willem A.
Perris, Hjördis *See* Arrindell, Willem A.
——*See* Perris, C.
Perry, Paul J., Alexander, Bruce, Prince, Randall A. and Dunner, Frederick J. The utility of a single-point dosing protocol for predicting steady-state lithium levels 401
Peselow, Eric (C) *See* Levick, Stephen E.
Pico Soler, E. (C) *See* de Leon Molina, J.
Pihlajamäki, K. *See* Sylvalähti, E. K. G.
Pilowsky, I. (C) Research on the value of psychotherapy 337
Pocock, P. V. *See* Barrett, K.
Poletti, Alison *See* Jones, Kathleen
Price, Jane *See* Aveline, Mark
Price, Thomas R. *See* Robinson, Robert G.
Primrose, David A., Matmati, Rabia, Boyd, Elizabeth, Gosden, Christine and Newton, Marjorie Prevalence of the fragile X syndrome in an institution for the mentally handicapped 655
Prince, Randall A. *See* Perry, Paul J.
Pu, Tinnyunt, Mohamed, E., Imam, Kareema and El-Roey, Ali M. One hundred cases of hysteria in Eastern Libya: a socio-demographic study (*Brief report*) 606

Quarrell, O. W. J. and Harper, Peter S. (C) Huntington's chorea without dementia 612

Rahill, Martin (C) *See* O'Shea, Brian
Rajkhowa, Sudhir *See* Singh, T. Hari
Rameshwari Singh, K *See* Cowie, Valerie A.
Reid, K. *See* Kutcher, S. P.
Renvoize, E. B. and Jain, J. Anniversary reactions (*Brief report*) 322
Reynolds, E. H. *See* Brown, S. W.
Riley, Alan J. and Riley, Elizabeth (C) Cyproheptadine and anti-depressant induced anorgasmia 217
Riley, Elizabeth J. (C) *See* Riley, Alan J.
Rizzoli, Antonio A. (C) Psychiatric disturbances in the shy-drager syndrome 484
Roberts, Keith and Vass, Neil Schneiderian first rank symptoms caused by benzodiazepine withdrawal (*Brief report*) 593
Robinson, Gilliam *See* Kendler, Kenneth S.
Robinson, Michael and Girish, Shetty (C) The Nottingham ECT study: double-blind? 747
Robinson, Robert G., Bolla-Wilson, Karen, Kaplan, Edith, Lipsey, John R. and Price, Thomas R. Depression influences intellectual impairment in stroke patients 541
Rollin, Henry R. *A Hundred Years Ago* 108, 197, 484
Ron, Maria A. Volatile substance abuse: a review of possible long-term neurological, intellectual and psychiatric sequelae (*Review article*) 235
Rosenman, Stephen J. and Tayler, Helen Mania following bereavement: a case report (*Brief report*) 468
Ross, M. W. *See* Clayer, J. R.
Rosenthal, Norman E. and James, Steven P. (C) Seasonal affective disorder 479

Sacchetti, E. *See* Faravelli, C.
Säkö, E. *See* Syvälahti, E. K. G.
Salkovskis, Paul M., Jones, David R. O. and Clark, David M. Respiratory control in the treatment of panic attacks: replication and extension with concurrent measurement of behaviour and pCO_2 526
Sampath, G. *See* Krska, Janet
Sashidharan, S. P. *See* Ingham, J. G.
——, and **Lipsedge, M.** (C) Schizophrenia and ethnicity 484
——, *See* Surtees, P. G.
——*See* McC. Miller, P.
Scheftner, William A. *See* Young, Michael A.
Scheinin, M. *See* Syvälahti, E. K. G.
Schmidt, L. G., Grohmann, R., Müller-Oerlinghausen, B., Ochsenfahrt, H. and Schönhöfer, P. S. Adverse drug reactions to first- and second-generation antidepressants; a critical evaluation of drug surveillance data 38
Schneider, John A. (C) *See* Luka, Laszlo P.

Schofield, A. (C) Capgras syndrome 750
Schönhöfer, P. S. *See* Schmidt, L. G.
Schrank-Fernandez, Candy *See* MacCarthy, Brigid
Sensky, Tom The general hospital psychiatrist: too many tasks and too few roles? 151
Shafran, Bronislava *See* Merskey, Harold
Shah, A. *See* Krska, Janet
Shalev, Arieh and Munitz, Hanan Conversion without hysteria: A case report and review of the literature 198
Shaw, David M. (C) *See* Watkins, Sarah E.
Shelley, R. K. (C) Lithium and piroxicam 343
Shulman, K. I. *See* Kutcher, S. P.
Silva, Joseph Jr. *See* Kronfol, Ziad
Silverman, Maurice (C) Anorexia nervosa: drop-outs from treatment 108
Sinanan, Kenneth and Haughton, Helen Evolution variants of the Munchausen syndrome (*Brief report*) 465
Singh, Iqbal and Zolese, G. (C) Is mania really incompatible with Down's syndrome? 613
Singh, K. Rameshwari *See* Cowie, Valerie A.
Singh, T. Hari and Rajkowa, Sudhir 49, XXXXY chromosome anomaly: an unusual variant of Klinefelter's syndrome (*Brief report*) 209
Sireling, L. I. and Paykel, E. S. (C) Depression in general practice 334
Smith, Andrew C. (C) Misprint of the year 344
Smith, A. H. W. *See* Esparon, J.
Smith, E. B. O. *See* Mayou, Richard
Smith, S. E. *See* Ghodse, A. H.
Snaith, R. P., Harrop, F. M., Newby, D. A. and Teale, C. Grade scores of the Montgomery Åsberg depression and the clinical anxiety scales (*Brief report*) 599
Soni, S. D. *See* Krska, Janet
Southmayd, S. E., Cairns, J., Delva, N. J., Letemendia, F. J. J. and Brunet, D. G. (C) Awake, perchance asleep? 749
Spalding, E. (C) *See* Abou-Saleh, M. T.
Spellman, Mary P. *See* Kendler, Kenneth S.
Spencer, John (C) The use of SRQ-20 in primary care situations 480
Srinath, Shoba *See* Andrade, Chittaranjan
Standish-Barry, H. M. A. S., Bouras, N., Hale, A. S., Bridges, P. K. and Bartlett, J. R. Ventricular size and CSF transmitter metabolite concentrations in severe endogenous depression 386
Stapleton, John *See* Ghodse, Hamid
Stefanis, Costas *See* Papakostas, Yiannis
Sturgeon, D. (C) *See* Leff, J.
Sturt, E. *See* Wykes, Til
Surtees, P. G. *See* Ingham, J. G.
——, **Sashidharan, S. P. and Dean, C.** Affective disorder amongst women in the general population: a longitudinal study 176
——*See* McC. Miller, P.
Syvälahti, E. K. G., Säkö, E., Scheinin, M., Pihlajamäki, K. and Hietala, J. Effects of intravenous and subcutaneous administration of apomorphine on the clinical symptoms of chronic schizophrenics 204

Takahashi, Saburo (C) *See* Chiba, Shigeru
Tarsh, Michael J. (C) On serious violence during sleep-walking 476
Tayler, Helen *See* Rosenman, Stephen J.
Teale, C. *See* Snaith, R. P.
Teasdale, John D. *See* Hooley, Jill M.
ten Horn, Sineke G. H. M. M. *See* de Jong, Joop T. V. M.
Tennant, C. *See* Chung, R. K.
Thiels, Cornelia (C) Epilepsy, psychosis, Kraepelin and Bleuler 107
Thomas, C. J. (C) Mental Health Act and medical treatment without consent 340
Thomas, Philip *See* Fraser, William I.
Tidmarsh, Simon F. (C) *See* Watkins, Sarah E.
Trimble, Michael R. Positive and negative symptoms in psychiatry (*Comment*) 587
Tsutomu, Miyagishi (C) *See* Chiba, Shigeru
Turnbull, Craig D. *See* Davidson, Jonathan
Tyrer, Peter *See* Kingdon, David

Vaidya, A. K. *See* Kumar, Anand
van der Ende, Jan *See* Arrindell, Willem A.
——*See* Perris, C.
Van Praag, M. M. *See* De Cuyper, H.
Varadaraj, R. and Mendonca, J. D. (C) Blood alcohol survey in patients with self-poisoning 615
Vass, Nell *See* Roberts, Keith
Vaughn, Christine (C) *See* Leff, Julian
Venulet, A. *See* Vlissides, Dimitrios N.
Verstraeten, D. *See* De Cuyper H.
Vita, A. *See* Faravelli, C.
Vlissides, Dimitrios N., Venulet, A. and Jenner, F. A. A double-blind gluten-free/gluten-load controlled trial in a secure ward population 447
von Knorring, Lars *See* Arrindell, Willem A.
——*See* Perris, C.

Waldron, G. *See* Gard, P. R.
Watkins, Sarah E., Clifford, Michael A., Tidmarsh, Simon F., Cowie, Valerie E., Shaw, David M., Ah-Sing, Eric and Dickerson, John W. T. (C) Plasma amino acids, Down's syndrome and dementia 339
Watson, J. P. *See* Al-Khani, M. A. F.
Weinberg, Warren, Emslie, Graham and Wilkes, Christopher (C) Depression in school phobia 335
West, C. *See* Alder, E. M.
Wexler, Bruce E. A model of brain function: its implications for psychiatric research (*Annotation*) 357
Whalley, L. J. *See* Christie, J. E.
Wheater, Richard *See* Cowie, Valerie A.
White, A. C. *See* Pai, M.
Wilkes, Chris (C) *See* Weinberg, Warren
Wilkinson, Greg and Williams, Paul Development of scales to measure treatment attitudes in psychiatry 581
Williams, Paul *See* Wilkinson, Greg 581
——*See* Mari, Jair de Jesus
Woggon, B. *See* Bobon, D.
Woodruff, Peter *See* Cameron, Lillian
Wooff, Kate *See* Dick, Barbara M.

Wykes, Til and Sturt, E. The measurement of social behaviour in psychiatric patients: an assesment of the reliability and validity of the SBS schedule 1

Yeragani, V. K. (C) *See* Keshavan, M. S.
Young, John *See* Harris, Brian
Young, Michael A., Scheftner, William A., Klerman, Gerald L., Andreasen, Nancy C. and Hirschfeld, Robert M. A. The endogenous sub-type of depression: a study of its internal construct validity 257

Zolese, G. (C) *See* Singh, Iqbal

PART III—BOOK REVIEWS

ALCOHOLISM

World Health Organization and Alcohol, Drug Abuse and Mental Health Administration: Mental Disorders, Alcohol and Drug-Related Problems: International Perspectives on their Diagnosis and Classification 755
Zimberg, Sheldon, Wallace, John and Blume, Sheila (Eds.): Practical Approaches to Alcoholism Psychotherapy. 2nd edition 490

BEHAVIOUR THERAPY

Hersen, Michel (Ed.): Practice of Inpatient Behavior Therapy: A Clinical Guide 352
Kendall, Philip C. (Ed.): Advances in Cognitive—Behavioral Research and Therapy. Vol. 4. 346
Turner, Samuel M. (Ed.): Behavioral Theories and Treatment of Anxiety 621

BEHAVIOURAL SCIENCE

Donovan, Bernard T.: Hormones and Human Behavior 760

BEREAVEMENT

Osterweis, Marian, Solomon, Frederic and Green, Morris: Bereavement: Reactions, Consequences and Care 349

BORDERLINE SYNDROME

Meissner, W. W.: The Borderline Spectrum: Differential Diagnosis and Developmental Issues 110

CHILDREN AND ADOLESCENTS

Branthwaite, Alan and Rogers, Don (Eds.): Children Growing Up 112
Connell, H. M.: Essentials of Child Psychiatry. 2nd edition 222
McMahon, Robert J. and Peters, Ray DeV (Eds.): Childhood Disorders: Behavioral-Developmental Approaches 622
Massie, Henry N. and Rosenthal, Judith: Childhood Psychosis in the First Four Years of Life 223
Schetkey, Diane H. and Benedek, Elissa P. (Eds.): Emerging Issues in Child Psychiatry and the Law 757
Schiffer, Mortimer: Children's Group Therapy: Methods and Case Histories 222
Sigman, Marian (Ed.): Children with Emotional Disorders and Developmental Disabilities: Assessment and Treatment 621
Stone, F. H. and Koupernik, C.: Child Psychiatry for Students. 2nd edition 355
Tabin, Johanna Krout: On the Way to Self: Ego and Early Oedipal Development 351

DEPRESSION

Lewinsohn, Peter M., Antonuccio, David O., Steinmetz, Julia L. and Teri, Linda: The Coping with Depression Course 112

DIAGNOSIS, MANAGEMENT AND TREATMENT

Greist, John H., Jefferson, James W. and Spitzer, Robert L. (Eds.): Treatment of Mental Disorders 353
Mavissakalian, Matig, Turner, Samuel M. and Michelson, Larry (Eds.): Obsessive-Compulsive Disorder: Psychological and Pharmacological Treatment 223
Meissner, W. W.: The Borderline Spectrum: Differential Diagnosis and Developmental Issues 110

DOWN'S SYNDROME

Lane, David and Stratford, Brian (Eds.): Current Approaches to Down's Syndrome 353

DRUG TREATMENT

Burrows, Graham D., Norman, Trevor R. and Davies, Brian (Eds.): Antipsychotics (Drugs in Psychiatry, Vol. 3) 623
Lal, Harbans, Labella, Frank and Lane, John: Endocoids: Proceedings of an International Symposium held in Fort Worth, Texas 761
World Health Organization and Alcohol, Drug Abuse and Mental Health Administration: Mental Disorders, Alcohol and Drug-Related Problems: International Perspectives on their Diagnosis and Classification 755

EPIDEMIOLOGY

Eaton, William W. and Kessler, Larry C. (Eds.): Epidemiologic Field Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program 489

EPILEPSY

Trimble, Michael R (Ed.): The Psychopharmacology of Epilepsy 225

FAMILIES

Committee for the Family. Group for the Advancement of Psychiatry: The Family, the Patient and the Psychiatric Hospital 759

Henso, Sergio and Grose Nellie P. (Eds.): Principles of Family Systems in Family Medicine 758

GENERAL HEALTH

World Health Organization: Targets for Health for All 489

GENERAL PSYCHIATRY

Goldman, H. H. (Ed.): General Psychiatry 350
Granville-Grossman, Kenneth (Ed.): Recent Advances in Clinical Psychiatry. Vol. 5 110
Greist, John H., Jefferson, James W. and Spitzer, Robert L. (Eds.): Treatment of Mental Disorders 353
Ingram, I. M., Timbury, G. C. and Mowbray, R. M.: Notes on Psychiatry. 6th edition 489
Kaplan, Harold I. and Sadock, Benjamin J. (Eds.): Comprehensive Textbook of Psychiatry. 4th edition 355
—— —— Study Guide and Self-Examination Review for Modern Synopsis of Comprehensive Textbook of Psychiatry IV. 2nd edition 485
Maguire, James, McKeon, Patrick and Power, Kieran Multiple Choice Questions in Psychiatry 623
Masterson, James F. (Ed.): The Real Self: A Developmental, Self and Object Relations Approach 754
Pichot, P., Berner, B., Wolf, R. and Thau, K. (Eds.): Psychiatry: The State of the Art. No. 5. Child and Adolescent Psychiatry, Mental Retardation and Geriatric Psychiatry 754
Ramon, Shulamit: Psychiatry in Britain: Meaning and Policy 485
Rose, F. Clifford (Ed.): Modern Approaches to the Dementias: I. Etiology and Pathophysiology. II. Clinical and Therapeutic Aspects 760
Shepherd, Michael (Ed.): Handbook of Psychiatry, Vol. 5. The Scientific Foundations of Psychiatry 617
Szasz, Thomas: The Therapeutic State: Psychiatry in the Mirror of Current Events 352

GERIATRIC DISORDERS

Butler, Alan (Ed.): Ageing: Recent Advances and Creative Responses 489
Gottfries, C. G. (Ed.): Normal Aging, Alzheimer's Disease and Senile Dementia—Aspects on Etiology, Pathogenesis, Diagnosis and Treatment 757
Jenike, Michael A.: Handbook of Geriatric Psychopharmacology 488

HISTORICAL

Gay, Peter: Freud for Historians 619
Isbister, J. N.: Freud: An Introduction to His Life and Work 620

LEGAL

Roth, Martin and Bluglass, Robert (Eds.): Psychiatry, Human Rights and the Law 345
Schetkey, Diane H. and Benedek, Elissa P. (Eds.): Emerging Issues in Child Psychiatry and the Law
Van Hoose, William and Kottler, Jeffrey A.: Ethical and Legal Issues in Counselling and Psychotherapy. 2nd edition 761

MENTAL HEALTH SERVICES

Freeman, H. L., Fryers, T. and Henderson, J. H.: Mental Health Services in Europe: Ten Years On 756

NEUROANATOMY

Fitzgerald, M. J. T.: Neuroanatomy: Basic and Applied 488

NEUROLOGY

Pincus, Jonathan H. and Tucker, Gary J.: Behavioural Neurology 491
Strub, Richard L. and Black, William: The Mental Status Examination in Neurology. 2nd edition 221

POLITICAL

Glass, James M.: Delusion: Internal Dimensions of Political Life 491
Levine, Murray: The History of Politics of Community Mental Health 759

POST-TRAUMATIC STRESS DISORDER

Hendin, Herbert and Haas, Ann Pollinger: Wounds of War: The Psychological Aftermath of Combat in Vietnam 354
Kelly, William E. (Ed.): Post-traumatic Stress Disorder and the War Veteran Patient 354

PSYCHOANALYSIS

Kohut, Heinz: How Does Analysis Cure? 224
Rycroft, Charles: Psychoanalysis and Beyond 490
Strean, Herbert S. (Ed.): Psychoanalytic Approaches to the Resistant and Difficult Patient 350
Tabin, Johanna Krout: On the Way to Self: Ego and Early Oedipal Development 351

PSYCHOLOGY

Holland, Norman N.: The I. 109
Neimeyer, Robert A.: The Development of Personal Construct Psychology 225
Simons, Richard C. (Ed.): Understanding Human Behaviour in Health and Illness 349
Steere, Jane: Ethics in Clinical Psychology 224
Watson, M. and Morris, T. (Eds.): Psychological Aspects of Cancer 113
Watts, Fraser N. (Ed.): New Developments in Clinical Psychology 486

PSYCHOPATHOLOGY

Hamilton, Max (Ed.): Fish's Clinical Psychopathology. 2nd edition 490
Pichot, P., Berner, P., Wolf, R. and Thau, K. (Eds.): Psychiatry: The State of the Art. I. Clinical Psychopathology, Nomenclature and Classification 347

Simons, Richard C. (Ed.): Understanding Human Behavior in Health and Illness 349

PSYCHOPHARMACOLOGY

Jenike, Michael A.: Handbook of Geriatric Psychopharmacology 488

Pichot, P., Berner, P., Wolf, R. and Thau, K. (Eds.): Psychiatry: The State of the Art. 3. Pharmacopsychiatry 348

Sandler, Merton and Silverstone, Trevor (Eds.): Psychopharmacology and Food 759

Trimble, Michael R. (Ed.): The Psychopharmacology of Epilepsy 225

PSYCHOPHYSIOLOGY

Gale, Anthony and Edwards, John A. (Eds.): Physiological Correlates of Human Behaviour. Vol. 1: Basic Issues. Vol. 2: Attention and Performance. Vol. 3: Individual Differences and Psychopathology 220

Saletu, B., Perris, C. and Kemali, D. (Eds.): Neurophysiological Correlates of Mental Disorders 759

PSYCHOSEXUAL

Segraves, R. Taylor and Haeberle, Erwin J. (Eds.): Emerging Dimensions of Sexology: Selected Papers from the Sixth World Congress 111

PSYCHOTHERAPIES

Casement, Patrick: On Learning from the Patient 114

Cocks, Geoffrey: Psychotherapy in the Third Reich: The Göring Institute 345

Dryden, Windy (Ed.): Individual Therapy in Britain 111

Friedman, Maurice: The Healing Dialogue in Psychotherapy 487

Hadley, Norman: Foundations of Aversion Therapy 621

Leuner, Hanscarl: Guided Affective Imagery: Mental Images in Short-Term Psychotherapy 487

Pichot, P., Berner, P., Wolf, R. and Thau, K. (Eds.): Psychiatry: The State of the Art. 4. Psychotherapy and Psychosomatic Medicine 348

Schiffer, Mortimer: Children's Group Therapy: Methods and Case Histories 222

Slipp, Samuel: Object Relations: A Dynamic Bridge between Individual and Family Therapy 220

Stern, Mark E. (Ed.): Psychotherapy and the Religiously Committed Patient 111

Zimberg, Sheldon, Wallace, John and Blume, Sheila (Eds.): Practical Approaches to Alcoholism Psychotherapy. 2nd edition 490

RELIGIOUS ISSUES

Byrnes, Joseph F.: The Psychology of Religion 622

Stern, Mark E. (Ed.): Psychotherapy and the Religiously Committed Patient 111

RESEARCH

Cancro, Robert and Dean, Stanley B.: Research in the Schizophrenic Disorders: The Stanley R. Dean Award Lectures Vol II. 114

Helgason, T. (Ed.): The Long-Term Treatment of Functional Psychoses: Needed Areas of Research 622

SCHIZOPHRENIA

Cancro, Robert and Dean, Stanley R.: Research in the Schizophrenic Disorders: The Stanley R. Dean Award Lectures 114

SOCIAL AND COMMUNITY

Jones, L. Ralph and Parlour Richard R. (Eds.): Psychiatric Services for Underserved Rural Populations 759

Levine, Murray: The History of Politics of Community Mental Health 759

SOCIAL POLICY

Brown, Phil (Ed.): Mental Health Care and Social Policy 113

Ramon, Shulamit: Psychiatry in Britain: Meaning and Policy 485

SOCIAL PSYCHIATRY

Hudolin, Vladimir: Social Psychiatry 487

STRESS

Zales, Michael R. (Ed.): Stress in Health and Disease 488

TREATMENT

Turner, Samuel M. (Ed.): Behavioural Theories and Treatment of Anxiety 621

We would like to thank the following who have acted as specialist assessors of original papers

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INDEX TO VOLUME 154

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Index to Volume 154

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PART I – SUBJECTS 3–15
PART II – CONTRIBUTORS 15–22
PART III – BOOK REVIEWS 22–26
SUPPLEMENT 4, VOLUME 154 27–29
ACKNOWLEDGEMENT TO ASSESSORS 30–31

Abbreviations: BR Brief Report; C Correspondence; other abbreviations given in text of index.

PART I. SUBJECTS

A hundred years ago.
  Inebriate criminal responsibility. Henry Rollin 276–277
  Insomnia. Henry Rollin 890
  Medico-Psychological Association: certificate in Psychological Medicine – examination questions. Henry Rollin 578
  Medico-Psychological Association: Quarterly meeting. Henry Rollin 126
  The education of idiots and imbeciles. Henry Rollin 733
Absconders. Characteristics of psychiatric hospital absconders. Arden R. Tomison 368–371
Admissions.
  Admission trends. Gary Hosty (C) 731
  Psychiatric clinics in general practice: do they reduce admissions? Paul Williams and Matteo Balestrieri 67–71
Adolescence.
  A follow-up of adolescents with obsessive–compulsive disorder. M. Allsopp and C. Verduyn 829–834
  Childhood and adolescent depression. Peter Birleson (C) 267–268
  Teenage depressive stupor. Fuad Hassanyeh and Kenneth Davison (C) 567
Affective disorders.
  see also **Mood disorders**
  Affective disorders and cerebral vascular disease. Sergio E. Starkstein and Robert G. Robinson (*Review article*) 170–182
  Affective 'switch mechanisms'. Mamoun Mobayed (C) 884
  Bipolar affective disorder, causes and prevention of relapse. Trevor Silverstone and Sarah Romans-Clarkson (*Review article*) 321–335
  The switch mechanism and the bipolar/unipolar dichotomy. M. W. P. Carney *et al* 48–51
Agranulocytosis. Two cases of agranulocytosis on addition of a butyrophenone to a long-standing course of phenothiazine treatment. Allan Young and Robert Kehoe (BR) 710–712
AIDS.
  see also **HIV**
  AIDS as a current psychopathological theme: a report on five heterosexual patients. John Todd (BR) 253–255
  Health education and the AIDS epidemic. Leon Eisenberg 754–767
  Munchausen syndrome masquerading as AIDS-induced depression. J. McDonald and K. Wafer (C) 420–421
  Organic reaction in AIDS. G. L. Milner (BR) 255–257
  Psychosocial status of 192 out-patients with HIV infection and AIDS. Michael B. King 237–242
Akathisia. A rating scale for drug-induced akathisia. Thomas R. E. Barnes 672–676
Akinesia. Gilles de la Tourette's syndrome: amelioration following acute akinesia during lorazepam withdrawal. Simon Wright and Malcolm Peet (BR) 257–259
Alcoholism.
  As the years go rolling by: drinking problems in the time dimension. Griffith Edwards (*Benno Pollak Lecture 1988*) 18–26
  Inebriate criminal responsibility. Henry Rollin (*A hundred years ago*) 276–277

- Quality of parenting in alcoholics and narcotic addicts. Elsa Bernardi *et al* 677–682
- Severity of withdrawal in subjects exposed to a combination of alcohol and minor tranquillisers. Christopher S. Thomas *et al* 83–85
- Wernicke's encephalopathy in an 18-year-old woman. Stuart Turner *et al* (BR) 261–262

Alexithymia.
- Alexithymia, masked depression and loss in a holocaust survivor. Robert Z. Fisch (BR) 708–710
- Psychological-mindedness and the alexithymia construct. Graeme Taylor *et al* (C) 731–732

Alzheimer's disease.
- Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function. R. Hunter *et al* 790–796
- Genetics, Alzheimer's disease and senile dementia. D. W. K. Kay (*Review article*) 311–320
- The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type. Barbara Sahakian *et al* 797–800

Annotations.
- Monoamine oxidase inhibitors: rehabilitation from recent research? David Nutt and Paul Glue 287–291
- Sight and insight: brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography. John L. Waddington 433–436
- Viruses, immunity and mental disorder. David J. King and Stephen J. Cooper 1–7

Anorexia nervosa.
- Anorexia nervosa in Hong Kong: why not more Chinese? Sing Lee *et al* 683–688
- Perceptivity and paraperceptivity during measurement of gastric emptying in anorexia and bulimia nervosa. P. H. Robinson 400–405
- Photography for anorexia nervosa. D. M. Hambridge (C) 575
- The validity of the eating disorder examination and its subscales. Zaffra Cooper *et al* 807–812

Anticholinergics. Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana. Rajiv Tandon *et al* (BR) 712–714

Antidepressants. The toxicity of antidepressants. George Beaumont (*Comment*) 454–458

Antipsychotics. Tea and antipsychotics. John Collier (C) 276

Anxiety disorders.
- Frequency of symptoms in melancholia (depressive illness). M. Hamilton 201–206
- Monoamine oxidase inhibitors: rehabilitation from recent research? David Nutt and Paul Glue (*Annotation*) 287–291
- Nosological problems. C. G. Ballard (C) 730
- Prevalence of benzodiazepine abuse and dependence in psychiatric in-patients with different nosology: an assessment of hospital-based drug surveillance data. L. G. Schmidt *et al* 839–843
- The effects of childhood parental death and divorce on six-month history of anxiety disorders. J. Lindsey Tweed *et al* 823–828

Arson. Epilepsy and arson. Peter K. Carpenter and Alan L. King (BR) 554–556

'Asneezia'. 'Asneezia' – some further observations. G. D. Shukla 689–690

Asthma. Hyperventilation causing asthma (C) 576–577

Athletics. Illicit drug use in strength athletes. Precilla Choi and Andrew Parrott (C) 732–733

Attention. The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type. Barbara Sahakian *et al* 797–800

Benzodiazepines.
- Benzodiazepine addiction in heroin addicts. Rhodri Huws (C) 886
- Prevalence of benzodiazepine abuse and dependence in psychiatric in-patients with different nosology: an assessment of hospital-based drug surveillance data. L. G. Schmidt *et al* 839–843
- The damnation of benzopdiazepines. F. Kräupl Taylor (*Point of view*) 697–704

'Bhanamati'. 'Bhanamati' sorcery and psychopathology in South India: a clinical study. M. S. Keshavan *et al* 218–220

Binswanger's disease. Treatment of mood disorder associated with Binswanger's disease. Eileen M. Joyce and Raymond Levy (BR) 259–261

'Biological' treatment. 'Biological' treatment. E. D. Myers (C) 120–121

Bipolar affective disorder. Bipolar affective disorder, causes and prevention of relapse. Trevor Silverstone and Sarah Romans-Clarkson (*Review article*) 321–335

Bipolar/unipolar dichotomy. The switch mechanism and the bipolar/unipolar dichotomy. M. W. P. Carney *et al* 48–51

Books reconsidered.
- *A Critical Dictionary of Psychoanalysis*: Charles Rycroft. (John Birtchnell) 734–737
- *A Study of Brief Psychotherapy*: D. H. Malan. (Jeremy Holmes) 891–893
- *Child Care and the Growth of Love*: John Bowlby. (Ann Gath) 579–580

Bowlby, John. *Child Care and the Growth of Love* (Ann Gath, *Books reconsidered*) 579–580

Brain damage. Neuronal misconnections and psychiatric disorder: is there a link? Robert Goodman (*Comment*) 292–299

Bromocriptine. Concomitant treatment of neuroleptic malignant syndrome and psychosis. Harry D. Goldwasser *et al* (BR) 102–104

Bulimia nervosa.
- Perceptivity and paraperceptivity during measurement of gastric emptying in anorexia and bulimia nervosa. P. H. Robinson 400–405
- The DST and TRH test in bulimia nervosa. A. S. Kaplan *et al* 86–92

The validity of the eating disorder examination and its subscales. Zaffra Cooper *et al* 807–812

Buspirone. Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Siobhan M. Murphy *et al* 529–534

Butyrophenone. Two cases of agranulocytosis on addition of a butyrophenone to a long-standing course of phenothiazine treatment. Allan Young and Robert Kehoe (BR) 710–712

Camberwell collaborative depression study. The Camberwell collaborative depression study. T. K. J. Craig and Elaine Murphy (C) 564–565, Peter McGuffin *et al* (C) 565

Capgras' syndrome.
- Capgras' syndrome. Shôn W. Lewis (C) 270–271, B. H. Green (C) 271, Bron Lipkin (C) 414
- Capgras' syndrome and folie à deux involving mother and child. J. Hart and G. M. G. McClure (BR) 552–554
- Capgras' syndrome and town duplication. Christopher Ball and Tim Exworthy (C) 889–890
- Delusions of inanimate doubles. S. F. Signer (C) 573

Cardiovascular disease. Prevention of cardiovascular disease by psychological methods. Derek W. Johnston (*Review article*) 183–194

Case conferences.
- A dementia syndrome of dependency. Roger Howells and Barbara Beats 872–876
- Thirty years' war: a battle with insomnia. J. R. Newton *et al* 691–696

Castration. Castration and the sexual offender. C. J. Hansen and J. Schioldann-Nielsen (C) 272

Cathexis. Self-cathexis and other-cathexis: vicissitudes in the history of an observation. D. Macdiarmid 844–852

Cerebral ventricles. Family history and cerebral ventricular enlargement in schizophrenia: a case control study. Michael J. Owen *et al* 629–634

Cerebrovascular disorders.
- Affective disorders and cerebral vascular disease. Sergio E. Starkstein and Robert G. Robinson (*Review article*) 170–182
- Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function. R. Hunter *et al* 790–796
- Mood disorder following cerebrovascular accident. M. R. Eastwood *et al* 195–200

Childbirth. Non-psychotic psychiatric disorder after childbirth. Brice Pitt (C) 119–120, Paul-Allan Dewsnap and George Stein (C) 120

Childhood.
- Capgras' syndrome and folie à deux involving mother and child. J. Hart and G. M. G. McClure (BR) 552–554
- *Child Care and the Growth of Love*: John Bowlby. (Ann Gath, *Books reconsidered*) 579–580
- Childhood and adolescent depression. Peter Birleson (C) 267–268
- Children surviving parental murder. Noel McClune and Patricia Donnelly (C) 889
- Maternal depression and the emotional development of the child. H. L. Caplan *et al* 818–822
- Pre-pubertal depressive stupor. Lorne B. Warneke (C) 418–419
- Significance of extreme temperament in infancy for clinical status in pre-school years.
  - I: Value of extreme temperament at 4–8 months for predicting diagnosis at 4.7 years. Michel Maziade *et al* 535–543
  - II: Patterns of temperament change and implications for the appearance of disorders. Michel Maziade *et al* 544–551
- The effects of childhood parental death and divorce on six-month history of anxiety disorders. J. Lindsey Tweed *et al* 823–828

Cholinergic syndrome. Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana. Rajiv Tandon *et al* (BR) 712–714

Clomipramine. Hyponatraemia and clomipramine therapy. D. R. Pledger and H. Mathew (BR) 263–264

Clonidine.
- Naltrexone and clonidine in heroin withdrawal treatment. D. Colin Drummond and Douglas Turkington (C) 571–572, Colin Brewer (C) 572
- Tricyclic wash-out and growth hormone response to clonidine. M. Schittecatte *et al* 858–863

Cognition. Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function. R. Hunter *et al* 790–796

Cognitive therapy. An uncontrolled study of cognitive therapy for morbid jealousy. N. R. Bishay *et al* 386–389

Comments.
- Community care and the difficult and offender patient. T. D. Scannell 615–619
- Neuronal misconnections and psychiatric disorder: is there a link? Robert Goodman 292–299
- The toxicity of antidepressants. George Beaumont 454–458
- The womb lay still in ancient Egypt. Harold Mersky and Paul Potter 751–753

Community care.
- Chronic patients in acute wards. P. M. Abbott *et al* (C) 730
- Community care and the difficult and offender patient. T. D. Scannell (*Comment*) 615–619
- Community management of schizophrenia: a two-year follow-up of a behavioural intervention with families. Nicholas Tarrier *et al* 625–628
- Day-hospital and community treatment for acute psychiatric illness: a critical appraisal. Francis Creed *et al* (*Review article*) 300–310
- The chronically mentally ill in community facilities: a study of quality of life. C. J. Simpson *et al* 77–82

Computerised tomography.
- CT studies of schizophrenia. C. Mundt (C) 413
- Sample size and CT scans in schizophrenia. S. W. Lewis (C) 268–269

- Scottish first episode schizophrenia study. VI. Computerised tomography brain scans in patients and controls. Scottish schizophrenia research group 492–498

Consciousness. Altered state of consciousness in a compulsive water drinker. Sing Lee *et al* (BR) 556–558

Conversion disorders. Conversion disorders and ECT. Walter F. Daniel *et al* (C) 274–275

Corrigenda.
- December 1988, **153,** 796 (N. Kreitman and P. Casey). 733
- December 1988, **153,** 850 (R. J. Russell). 421
- September 1988, **153,** 355 (R. Manchandra *et al*). 421

Creatinine phosphokinase.
- Concomitant treatment of neuroleptic malignant syndrome and psychosis. Harry D. Goldwasser 102–104
- CPK levels and neuroleptic malignant syndrome. Hari D. Maharajh (C) 885–886

Criminal responsibility. Inebriate criminal responsibility. Henry Rollin (*A hundred years ago*) 276–277

Current literature. Comments on the Northwick Park 'functional' psychosis study. G. M. Goodwin *et al* 406–409

Day hospitals.
- Day-hospital and community treatment for acute psychiatric illness: a critical appraisal. Francis Creed *et al* (*Review article*) 300–310
- Treatment of severe psychiatric illness in a day hospital. Francis Creed *et al* 341–347

De Clérambault's syndrome. De Clérambault's syndrome (erotomania) in organic delusional syndrome. Y. Y. El Gaddal (BR) 714–716

Delusions.
- De Clérambault's syndrome (erotomania) in organic delusional syndrome. Y. Y. El Gaddal (BR) 714–716
- Delusional depression in 19th-century Scotland. Andrew Robinson (C) 573–574.
- Delusions of inanimate doubles. S. F. Signer (C) 573
- Delusions of pregnancy in men: case report and review of the literature. Santosh K. Chaturvedi (BR) 716–718

Dementia.
- A dementia syndrome of dependency. Roger Howells and Barbara Beats (*Case conference*) 872–876
- Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function. R. Hunter *et al* 790–796
- Dementia and Parkinson's disease. W. R. G. Gibb (*Review article*) 596–614
- Dexamethasone suppression test in dementia and depression: clinical and biological correlates. J. Shrimankar *et al* 372–377
- Eating habits in dementia: a descriptive study. Charles H. Morris *et al*, 801–806
- Genetics, Alzheimer's disease and senile dementia. D. W. K. Kay (*Review article*) 311–320
- Prevalence of dementia. D. W. K. Kay (C) 121–122
- The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type. Barbara Sahakian *et al* 797–800

Dependency. A dementia syndrome of dependency. Roger Howells and Barbara Beats (*Case conference*) 872–876

Depression.
- Alexithymia, masked depression and loss in a holocaust survivor. Robert Z. Fisch (BR) 708–710
- Camberwell collaborative depression study. T. K. J. Craig and Elaine Murphy (C) 564–565, Peter McGuffin *et al* (C) 565
- Childhood and adolescent depression. Peter Birleson (C) 267–268
- Chronic depression. R. Thomas (C) 124–125
- Delusional depression in 19th-century Scotland. Andrew Robinson (C) 573–574.
- Depression in attempted suicide. Robert D. Goldney (C) 881–882
- Depression following spinal cord injury: a prospective in-patient study. Fiona K. Judd *et al* 668–671
- Depression in self-harm patients. Jon Ennis *et al* 41–47
- Dexamethasone suppression test in dementia and depression: clinical and biological correlates. J. Shrimankar *et al* 372–377
- Frequency of symptoms in melancholia (depressive illness). M. Hamilton 201–206
- History of depressive disorder. W. H. Goss (C) 122
- Maternal depression and the emotional development of the child. H. L. Caplan *et al* 818–822
- Monoamine oxidase inhibitors: rehabilitation from recent research? David Nutt and Paul Glue (*Annotation*) 287–291
- Munchausen syndrome masquerading as AIDS-induced depression. J. McDonald and K. Wafer (C) 420–421
- Nosological problems. C. G. Ballard (C) 730
- Poverty of speech in schizophrenia and depression during in-patient and post-hospital periods. Ann Barnett Ragin *et al* 52–57
- Pre-pubertal depressive stupor. Lorne B. Warneke (C) 418–419
- Prevalence of benzodiazepine abuse and dependence in psychiatric in-patients with different nosology: an assessment of hospital-based drug surveillance data. L. G. Schmidt *et al* 839–843
- Social support and the outcome of major depression. Linda K. George *et al* 478–485
- Teenage depressive stupor. Fuad Hassanyeh and Kenneth Davison (C) 567
- The hormonal environment of post-natal depression. Brian Harris *et al* 660–667
- The nature and prevalence of depression in chronic schizophrenic in-patients. Thomas R. E. Barnes *et al* 486–491
- The occurrence of depression following mania: a method of predicting vulnerable cases. C. P. Lucas *et al* (BR) 705–708
- The relationship between depression and hopelessness: implications for current theories of depression. Sheila M. Greene 650–659
- The toxicity of antidepressants. George Beaumont (*Comment*) 454–458

  The use of rating scales to identify post-natal depression. Brian Harris *et al* 813–817
  Treatment of suicidal manic depression. Hameen Markar (C) 123–124
  What's so special about two years anyway? Paul Bridges (C) 884–885
  Which depressed patients will respond to electroconvulsive therapy? The search for biological predictors of recovery. Allan I. F. Scott (*Review article*) 8–17
  Which patients will respond to ECT? Lakshmi N. Yatham *et al* (C) 879, Allan Scott (C) 879–880

Detoxification. Circumstances surrounding the initial lapse to opiate use following detoxification. Brendan P. Bradley *et al* 354–359

Dexamethasone suppression test (DST).
  Dexamethasone suppression test in dementia and depression: clinical and biological correlates. J. Shrimankar *et al* 372–377
  The DST and TRH test in bulimia nervosa. A. S. Kaplan *et al* 86–92

Diazepam. Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Siobhan M. Murphy *et al* 529–534

Disease.
  Molecular genetics and ethics. M. F. Bristow (C) 882
  Molecular genetics and human disease. Anthony S. David (C) 119

Divorce. The effects of childhood parental death and divorce on six-month history of anxiety disorders. J. Lindsey Tweed *et al* 823–828

Dopamine receptors. Sight and insight: brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography. John L. Waddington (*Annotation*) 433–436

Drug use. Illicit drug use in strength athletes. Precilla Choi and Andrew Parrott (C) 732–733

Drugs, general *see* **Anticholinergics, Antidepressants, Antipsychotics, Lipids, Monoamine oxidase inhibitors, Narcotics, Neuroleptics, Opiates, Tranquillisers and Tricyclics**

Drugs, specific.
  Abuse *see* **Alcohol, Heroin** and **Marijuana**
  Investigations *see* **Creatinine phosphokinase, Dexamethasone, Nicotine** and **S-adenosyl methionine (SAM)**
  Therapy *see* **Benzodiazepines, Bromocriptine, Buspirone, Butyrophenone, Clomipramine, Clonidine, Diazepam, Lithium, Lofepramine, Lorazepam, Methadone, Mianserin, Naltrexone, Phenothiazine, Propofol** and **Zuclopenthixol**

Dyskinesia, tardive. see **Tardive dyskinesia (TD)**

Dysphonia, spastic. Spastic dysphonia and denervation signs in a young man with tardive dyskinesia. Jeffrey A. Lieberman and Ross Reife (BR) 105–109

Eating disorders.
  Eating habits in dementia: a descriptive study. Charles H. Morris *et al* 801–806
  Melatonin and sulphatoxymelatonin in eating disorder patients. S. H. Kennedy *et al* (C) 272–273
  The validity of the eating disorder examination and its subscales. Zaffra Cooper *et al* 807–812

Eccentrics.
  Elderly eccentrics. C. Powell (C) 724
  'Normal' eccentrics. David J. Weeks (C) 410–411

Egypt. The womb lay still in ancient Egypt. Harold Mersky and Paul Potter (*Comment*) 751–753

Electroconvulsive therapy (ECT).
  A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms. David Dodwell and David Goldberg 635–639
  Conversion disorders and ECT. Walter F. Daniel *et al* (C) 274–275
  ECT mythology? C. G. Ballard (C) 575
  EEG monitoring of ECT. Erica M. Jones (C) 880–881, Robin G. McCreadie (C) 881
  Failure to convulse with ECT. Gianetta Rands (C) 124, Ivan G. Schick (C) 125
  Is electroencephalographic monitoring of electroconvulsive therapy clinically useful? R. G. McCreadie *et al* 229–231
  Manic features during a course of ECT. Ken Barrett (C) 575
  The use of propofol for anaesthesia during ECT. K. H. Simpson and R. P. Snaith (C) 721–722
  Which depressed patients will respond to electroconvulsive therapy? The search for biological predictors of recovery. Allan F. Scott (*Review article*) 8–17
  Which patients will respond to ECT? Lakshmi N. Yatham *et al* (C) 879, Allan Scott (C) 879–880
  Would monitoring by electroencephalogram improve the practice of electroconvulsive therapy? Allan F. Scott *et al* 853–857

Electroencephalograms.
  EEG monitoring of ECT. Erica M. Jones (C) 880–881, Robin G. McCreadie (C) 881
  Is electroencephalographic monitoring of electroconvulsive therapy clinically useful? R. G. McCreadie *et al* 229–231
  Would monitoring by electroencephalogram improve the practice of electroconvulsive therapy? Allan F. Scott *et al* 853–857

Epilepsy. Epilepsy and arson. Peter K. Carpenter and Alan L. King (BR) 554–556

Erotomania.
  De Clérambault's syndrome (erotomania) in organic delusional syndrome. Y. Y. El Gaddal (BR) 714–716
  Homo-erotomania. Stephen F. Signer (C) 729

Ethics.
  Molecular genetics and ethics. M. F. Bristow (C) 882
  Molecular genetics and human disease. Anthony S. David (C) 119

Ethnic density. Ethnic density and schizophrenia. Roland Littlewood (C) 123

Expressed emotion (EE).
  A trial of family therapy v. a relatives group for schizophrenia. J. Leff *et al* 58–66

- Counselling the relatives of the long-term adult mentally ill.
  - I: Evaluation of the impact on relatives and patients. Brigid MacCarthy *et al* 768–775
  - II: A low-cost supportive model. Liz Kuipers *et al* 775–782
- Lithium prophylaxis and expressed emotion (EE). S. Priebe *et al* 396–399
- The initial onset of schizophrenia and family expressed emotion: some methodological considerations. Lois Imber Mintz *et al* 212–217

Family studies.
- A family study of two subgroups of schizoaffective patients. Mario Maj 640–643
- Family history and cerebral ventricular enlargement in schizophrenia: a case control study. Michael J. Owen *et al* 629–634
- Freud's family. Peter Reder (*Point of view*) 93–98
- Shoplifting in families of mentally handicapped persons. Meera Roy (C) 574

Family therapy.
- A trial of family therapy v. a relatives group for schizophrenia. J. Leff *et al* 58–66
- Community management of schizophrenia: a two-year follow-up of a behavioural intervention with families. Nicholas Tarrier *et al* 625–628
- Counselling the relatives of the long-term adult mentally ill.
  - I: Evaluation of the impact on relatives and patients. Brigid MacCarthy *et al* 768–775
  - II: A low-cost supportive model. Liz Kuipers *et al* 775–782
- Family therapy influences on general adult psychiatry. David Cottrell 473–477

Fear. The fear questionnaire. W. A. Arrindell (C) 725–726, Florence J. van Zuuren (C) 726–727

Folie à deux. Capgras' syndrome and folie à deux involving mother and child. J. Hart and G. M. G. McClure (BR) 552–554

Freud, Sigmund. Freud's family. Peter Reder. (*Point of view*) 93–98

Gastric emptying. Perceptivity and paraperceptivity during measurement of gastric emptying in anorexia and bulimia nervosa. P. H. Robinson 400–405

General practice.
- Admission trends. Gary Hosty (C) 731
- PROQSY: A computerised technique for psychiatric case identification in general practice. Greg Wilkinson and A. C. Markus 378–382
- Psychiatric clinics in general practice. Do they reduce admissions? Paul Williams and Matteo Balestrieri 67–71
- Psychotherapy and general practice. Linda Gask and Graeme McGrath (*Review article*) 445–453
- Referrals from general practitioners to psychiatrists and paramedical mental health professionals. Greg Wilkinson 72–76

Genetics.
- Genetics, Alzheimer's disease and senile dementia. D. W. K. Kay (*Review article*) 311–320
- Molecular genetics and human disease. Anthony S. David (C) 119
- The impact of molecular genetics on our understanding of the psychoses. Michael J. Mullan and Robin M. Murray (*Review article*) 591–595

Gilles de la Tourette syndrome.
- Gilles de la Tourette's syndrome: amelioration following acute akinesia during lorazepam withdrawal. Simon Wright and Malcolm Peet (BR) 257–259
- The Gilles de la Tourette syndrome: the current status. Mary M. Robertson (*Review article*) 147–169

Glasgow. The Glasgow rehabilitation survey. Martin G. Livingston and Adam Bryson 620–624

Globus hystericus. Is globus hystericus? Chris Mace *et al* (C) 727, I. J. Deary and Janet A. Wilson (C) 727–728

'Good old days'. 'Good old days' of psychiatry. Judy Harrison (C) 126

Group homes. The chronically mentally ill in community facilities: a study of quality of life. C. J. Simpson *et al* 77–82

Hallucinations. Lithium-induced paranoid hallucinatory state. S. H. Kamlana (C) 273

Health education. Health education and the AIDS epidemic. Leon Eisenberg 754–767

Heroin.
- Benzodiazepine addiction in heroin addicts. Rhodri Huws (C) 886
- Naltrexone and clonidine in heroin withdrawal treatment. D. Colin Drummond and Douglas Turkington (C) 571–572, Colin Brewer (C) 572
- Opiate withdrawal symptoms in response to 10-day and 20-day methadone withdrawal programmes. Michael Gossop *et al* 360–363
- Quality parenting in alcoholics and narcotic addicts. Elsa Bernardi *et al* 677–682

History taking. Taking a good history. Rajendra D. Persaud and Patricia H. Allderidge (C) 719–720

HIV.
- *see also* **AIDS**
- HIV screening. J. B. Connelly (C) 266–267
- Psychosocial status of 192 out-patients with HIV infection and AIDS. Michael B. King 237–242

Holmes, Sherlock. Elementary, my dear Freud. Michael Morris (C) 412–413

Holocaust. Alexithymia, masked depression and loss in a holocaust survivor. Robert Z. Fisch (BR) 708–710

Homicide. Women who kill their parents. P. T. d'Orban and Art O'Connor 27–33

Homo-erotomania. Homo-erotomania. Stephen F. Signer (C) 729

Hong Kong.
- Anorexia nervosa in Hong Kong: why not more Chinese? Sing Lee *et al* 683–688
- Suicide among Chinese schizophrenics in Hong Kong. K. K. Cheng *et al* 243–246

Hopelessness. The relationship between depression and hopelessness: implications for current theories of depression. Sheila M. Greene 650–659

Hormones.
- The DST and TRH test in bulimia nervosa. A. S. Kaplan *et al* 86–92
- The hormonal environment of post-natal depression. Brian Harris *et al* 660–667
- Tricyclic wash-out and growth hormone response to clonidine. M. Schittecatte *et al* 858–863

Hospitals.
- Characteristics of psychiatric hospital absconders. Arden R. Tomison 368–371
- Hospital suicides: are there preventable factors? Profile of the psychiatric hospital suicide. Seng Eng Goh *et al* 247–249
- Hospital suicides. Marcellino Smyth and Nick Craddock (C) 728, Robert Kehoe (C) 728–729
- Violent incidents in special hospitals. J. B. Coldwell and L. J. Naismith (C) 270

Hostility. Life events and hostility in self-poisoning. Roger Farmer and Francis Creed 390–395

Human experience. The varieties of human experience. John Nemiah (*Adolph Meyer lecture 1988*) 459–466

Hyperpyrexia. Malignant hyperpyrexia syndrome in combined treatment. E. F. Staufenberg and D. Tantam (C) 577–578

Hyperventilation. Hyperventilation causing asthma. Samuel I. Cohen (C) 576–577

Hyponatraemia.
- Hyponatraemia and clomipramine therapy. D. R. Pledger and H. Mathew (BR) 263–264
- Lofrepramine-induced hyponatraemia. K. R. Wylie *et al* (C) 419–420

Hysterectomy. Psychological aspects of hysterectomy: a prospective study. Margaret M. Ryan *et al* 516–522

Hysteria.
- Conversion disorders and ECT. Walter F. Daniel *et al* (C) 274–275
- Is globus hystericus? Chris Mace *et al* (C) 727, I. J. Deary and Janet A. Wilson (C) 727–728
- Self-cathexis and other-cathexis: vicissitudes in the history of an observation. D. Macdiarmid 844–852
- The womb lay still in ancient Egypt. Harold Mersky and Paul Potter (*Comment*) 751–753

Idiots and imbeciles. The education of idiots and imbeciles. Henry Rollin (*A hundred years ago*) 733

Immunity. Viruses, immunity and mental disorder. David J. King and Stephen J. Cooper (*Annotation*) 1–7

India.
- 'Bhanamati' sorcery and psychopathology in South India: a clinical study. M. S. Keshavan *et al* 218–220
- Factors associated with the course and outcome of schizophrenia in India: results of a two-year multicentre follow-up study. A Verghese *et al* 499–503
- Psychiatric disorders among medical in-patients in an Indian hospital. S. N. Deshpande *et al* 504–509

Information processing. The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type. Barbara Sahakian *et al* 797–800

Insomnia.
- Insomnia. Henry Rollin (*A hundred years ago*) 890
- Thirty years' war: a battle with insomnia. J. R. Newton *et al* (*Case conference*) 691–696

Jealousy, morbid. An uncontrolled study of cognitive therapy for morbid jealousy. N. R. Bishay *et al* 386–389

Journal supplements. Journal supplements. Matt Jelley (C) 121, Hugh Freeman (*Editor, British Journal of Psychiatry*) (C) 121

Korsakoff's psychosis. Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function. R. Hunter *et al* 790–796

Lectures.
- As the years go rolling by. Drinking problems in the time dimension. Griffith Edwards (*Benno Pollak lecture 1988*) 18–26
- The involvement of Soviet psychiatry in the persecution of dissenters. Anatoly Koryagin (*Quarterly meeting 1987*) 336–340
- The varieties of human experience. John Nemiah (*Adolph Meyer lecture 1988*) 459–466

Liaison service. The psychiatrist in the obstetric unit: establishing a liaison service. Louis Appleby *et al* 510–515

Life events. Life events and hostility in self-poisoning. Roger Farmer and Francis Creed 390–395

Lipids.
- Lipid-lowering drugs. Ian McLoughlin and Philip Clarke (C) 275–276
- Lipid-lowering drugs and violence. David F. Horrobin (C) 882–883

Listeria. Listeria and psychiatric syndromes. Janice M. Duncan (C) 887

Lithium.
- Lithium in pregnancy and still birth: a case report. S. K. Khandelwal *et al* (BR) 114–116
- Lithium prophylaxis and expressed emotion (EE). S. Priebe *et al* 396–399
- Lithium-induced paranoid hallucinatory state. S. H. Kamlana (C) 273

Lofepramine. Lofrepramine-induced hyponatraemia. K. R. Wylie *et al* (C) 419–420

Lorazepam. Gilles de la Tourette's syndrome: amelioration following acute akinesia during lorazepam withdrawal. Simon Wright and Malcolm Peet (BR) 257–259

Malan, D. H. *A Study of Brief Psychotherapy.* (Jeremy Holmes, *Books reconsidered*) 891–893

Mania.
- Manic features during a course of ECT. Ken Barrett (C) 575
- The occurrence of depression following mania: a method of predicting vulnerable cases. C. P. Lucas *et al* (BR) 705–708
- Treatment of suidical manic depression. Hameen Markar (C) 123–124

Marijuana. Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana. Rajiv Tandon *et al* (BR) 712–714

Maudsley, Henry. The Melbourne Maudsleys. George I. Szmukler (C) 887–888

Measles. Suspected SSPE – a delayed psychiatric presentation. Peter J. B. Mattinson (BR) 116–118

Medico-Psychological Association.
- Certificate in Psychological Medicine – examination questions. Henry Rollin (*A hundred years ago*) 578
- Quarterly meeting. Henry Rollin (*A hundred years ago*) 126

Melancholia.
- Frequency of symptoms in melancholia (depressive illness). M. Hamilton 201–206
- Nosological problems. C. G. Ballard (C) 730

Melatonin. Melatonin and sulphatoxymelatonin in eating disorder patients. S. H. Kennedy *et al* (C) 272–273

Melbourne. The Melbourne Maudsleys. George I. Szmukler (C) 887–888

Memory. The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type. Barbara Sahakian *et al* 797–800

Mental disorders. *see* **Psychiatric disorders**

Mental handicap. Shoplifting in families of mentally handicapped persons. Meera Roy (C) 574

Methadone.
- Benzodiazepine addiction in heroin addicts. Rhodri Huws (C) 886
- Opiate withdrawal symptoms in response to 10-day and 21-day methadone withdrawal programmes. Michael Gossop *et al* 360–363

Methodology. The initial onset of schizophrenia and family expressed emotion: some methodological considerations. Lois Imber Mintz *et al* 212–217

Mianserin. Involuntary movements associated with mianserin treatment: a case report. Koichi Otani *et al* (BR) 113–114

Mind–body. The mind–body problem. Jonathan Benjamin (C) 731

Molecular genetics.
- Molecular genetics and ethics. M. F. Bristow (C) 882
- Molecular genetics and human disease. Anthony S. David (C) 119

Monoamine oxidase inhibitors. Monoamine oxidase inhibitors: rehabilitation from recent research? David Nutt and Paul Glue (*Annotation*) 287–291

Mood disorders.
- *see also* **Affective disorders, Anxiety disorders, Bipolar affective disorders, Bipolar/unipolar dichotomy, Depression, Mania** and **Melancholia**
- Mood disorder following cerebrovascular accident. M. R. Eastwood *et al* 195–200
- Treatment of mood disorder associated with Binswanger's disease. Eileen M. Joyce and Raymond Levy (BR) 259–261

Movements, involuntary. Involuntary movements associated with mianserin treatment: a case report. Koichi Otani *et al* (BR) 113–114

Munchausen syndrome. Munchausen syndrome masquerading as AIDS-induced depression. J. McDonald and K. Wafer (C) 420–412

Naltrexone. Naltrexone and clonidine in heroin withdrawal treatment. D. Colin Drummond and Douglas Turkington (C) 571–572, Colin Brewer (C) 572

Narcotics. Quality of parenting in alcoholics and narcotic addicts. Elsa Bernardi *et al* 677–682

Near-death.
- Near-death experience. Sudhir Stokes (C) 567
- The near-death experience. Karl L. R. Jansen (C) 883–884

Neuroleptic malignant syndrome.
- Concomitant treatment of neuroleptic syndrome and psychosis. Harry D. Goldwasser *et al* (BR) 102–104
- CPK levels and neuroleptic malignant syndrome. Hari D. Maharajh (C) 885–886
- Malignant hyperpyrexia syndrome in combined treatment. E. F. Staufenberg and D. Tantam (C) 577–578
- Neuroleptic malignant syndrome and pneumomediastinum. Benjamin Hugh Green (BR) 560–561
- Zuclopenthixol-induced neuroleptic malignant syndrome at rechallenge and its extrapyramidal effects. Charles J. F. Kemperman (BR) 562–563.

Neuroleptics.
- Sight and insight: brain dopamine receptor occupancy by neuroleptics visualized in living schizophrenic patients by positron emission tomography. John L. Waddington (*Annotation*) 433–436
- The course of tardive dyskinesia in patients on long-term neuroleptics. J. A. Bergen *et al* 523–528

Neuronal misconnections. Neuronal misconnections and psychiatric disorders: is there a link? Robert Goodman (*Comment*) 292–299

Nicotine. The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type. Barbara Sahakian *et al* 797–800

Northwick Park. Comments on the Northwick Park 'functional' psychosis study. G. M. Goodwin *et al* (*Current literature*) 406–409

- **Notification.** Types of opiate addiction and notification to the Home Office. M. London and A. H. Ghodse 835–838

- **Obesity.** Tea and antipsychotics. John Collier (C) 276
- **Obsessive–compulsive disorders.**
  - A follow-up of adolescents with obsessive–compulsive disorder. M. Allsopp and C. Verduyn 829–834
  - Obsessive–compulsive rituals. Isaac Marks and Metin Basoglu (C) 565–567
- **Obstetric units.** The psychiatrist in the obstetric unit: establishing a liaison service. Louis Appleby *et al* 510–515
- **Offenders.** Community care and the difficult and offender patient. T. D. Scannell (*Comment*) 615–619
- **Old age.**
  - Elderly eccentrics. C. Powell (C) 724
  - Reflections on psychotherapy with ageing people, individually and in groups. A. Joan G. Hunter (*Point of view*) 250–252.
  - The natural history of mental disorder in old age, a long-term study. John R. Robinson 783–789
- **Opiates.**
  - Benzodiazepine addiction in heroin addicts. Rhodri Huws (C) 886
  - Circumstances surrounding the initial lapse to opiate use following detoxification. Brendan P. Bradley *et al* 354–359
  - Lapse, relapse and survival among opiate addicts after treatment: a prospective follow-up study. Michael Gossop *et al* 348–353
  - Opiate withdrawal symptoms in response to 10-day and 21-day methadone withdrawal programmes. Michael Gossop *et al* 360–363
  - The opiate prescribing debate. R. F. Hill (C) 888–889
  - Types of opiate addiction and notification to the Home Office. M. London and A. H. Ghodse 835–838
- **Organic delusional system.** De Clérambault's syndrome (erotomania) in organic delusional syndrome. Y. Y. El Gaddal (BR) 714–716

- **Panencephalitis.** Suspected subacute sclerosing panencephalitis (SSPE) – a delayed psychiatric presentation. Peter J. B. Mattinson (BR) 116–118
- **Panic attacks.** Respiratory control: its contribution to the treatment of panic attacks: a controlled study. George A. Hibbert and Michael Chan 232–236
- **Paradox.** Paradoxical intervention. Alistair J. Macdonald (C) 883
- **Paramedical personnel.** Referrals from general practitioners to psychiatrists and paramedical mental health professionals. Greg Wilkinson 72–76
- **Paranoid disorders.** Lithium-induced paranoid hallucinatory state. S. H. Kamlana (C) 273
- **Parasuicide.**
  - Depression in attempted suicide. Robert D. Goldney (C) 881–882
  - Depression in self-harm patients. J. Ennis *et al* 41–47
  - Parasuicide in young Asian women. Gyles Glover *et al* (C) 271–272
  - Repetition of parasuicide. Nigel Smeeton and Greg Wilkinson (C) 720, Normal Kreitman and Patricia Casey (C) 721
- **Parents.**
  - Children surviving parental murder. Noel McClune and Patricia Donnelly (C) 889
  - Quality of parenting in alcoholics and narcotic addicts. Elsa Bernardi *et al* 677–682
  - The effects of childhood parental death and divorce on six-month history of anxiety disorders. J. Lindsey Tweed *et al* 823–828
  - Women who kill their parents. P. T. d'Orban and Art O'Connor 27–33
- **Parkinson's disease.** Dementia and Parkinson's disease. W. R. G. Gibb (*Review article*) 596–614
- **Personality.** 'Normal' eccentrics. David J. Weeks (C) 410
- **Personality disorders.**
  - Defining personality disorder. T. J. Holden (C) 567–568, Scott O. Lilienfeld (C) 568–569
  - Multiple personality: a symptom of psychiatric disorder. Thomas A. Fahy *et al* (BR) 99–101
  - Multiple personality disorder. Onno van der Hart and Suzette Boon (C) 419, Jonathan E. A. Fleming (C) 877, Tom Fahy (C) 878
  - Psychiatrists' responses to personality disorder. C. Evans (C) 265–266, T. Widiger (C) 266
- **Phenothiazine.** Two cases of agranulocytosis on addition of a butyrophenone to a long-standing course of phenothiazine treatment. Allan Young and Robert Kehoe (BR) 710–712.
- **Philosophy.** Philosophy for trainees. C. Cabrera-Abreu (C) 575–576
- **Photography.** Photography for anorexia nervosa. D. M. Hambridge (C) 575
- **Pneumomediastinum.** Neuroleptic malignant syndrome and pneumomediastinum. Benjamin Hugh Green (BR) 560–561
- ***Points of view.***
  - 1. Psychiatric justice. Thomas Szasz 864–869
  - 2. Szasz of psychiatric justice. D. J. West 870–871
  - Freud's family. Peter Reder 93–98
  - Reflections on psychotherapy with ageing people, individually and in groups. A. Joan G. Hunter 250–252
  - The damnation of benzodiazepines. F. Kräupl Taylor 697–704
- **Poisoning.** Unsubstantiated complaints of being poisoned: psychopathology of patients being referred to the National Poisons Unit. E. A. Hutchesson and G. N. Volans 34–40
- **Positron emission tomography.** Sight and insight: brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography. John L. Waddington (*Annotation*) 433–436
- **Post-traumatic stress disorder.**
  - Post-traumatic stress. A. C. White (C) 886–887
  - The aetiology of post-traumatic morbidity: predisposing, precipitating and perpetuating factors. Alexander C. McFarlane 221–228

Pregnancy.
  Delusions of pregnancy in men: case report and review of the literature. Santosh K. Chaturvedi (BR) 716–718
  Lithium in pregnancy and still birth. A case report. S. K. Khandelwal *et al* (BR) 114–116
  Psychotic illness following termination of pregnancy. Kim Davidson and Anthony W. Clare (BR) 559–560
Prescribing. A comparison of in-patient and out-patient prescribing. D. N. Anderson 644–649
Primary prevention. Prevention of cardiovascular disease by psychological methods. Derek W. Johnston (*Review article*) 183–194
Propofol. The use of propofol for anaesthesia during ECT. K. H. Simpson and R. P. Snaith (C) 721–722
PROQSY. PROQSY: a computerised technique for psychiatric case identification in general practice. Greg Wilkinson and A. C. Markus 378–382
Psychiatric clinics.
  Admission trends. Gary Hosty (C) 731
  Psychiatric clinics in general practice: do they reduce admissions? Paul Williams and Matteo Balestrieri 67–71
Psychiatric disorders.
  Chronic patients in acute wards. P. M. Abbott *et al* (C) 730
  Counselling the relatives of the long-term adult mentally ill.
    I: Evaluation of the impact on relatives and patients. Brigid MacCarthy *et al* 768–775
    II: A low-cost supportive model. Liz Kuipers *et al* 775–782
  Day-hospital and community treatment for acute psychiatric illness: a critical appraisal. Francis Creed *et al* (*Review article*) 300–310
  Listeria and psychiatric syndromes. Janice M. Duncan (C) 887
  Molecular genetics and ethics. M. F. Bristow (C) 882
  Molecular genetics and human disease. Anthony S. David (C) 119
  Multiple personality: a symptom of psychiatric disorder. Thomas A. Fahy *et al* (BR) 99–101
  Neuronal misconnections and psychiatric disorder: is there a link? Robert Goodman (*Comment*) 292–299
  Non-psychotic psychiatric disorder after childbirth. Brice Pitt (C) 119–120, Paul-Allan Dewsnap and George Stein (C) 120
  Psychiatric disorders among medical in-patients in an Indian hospital. S. N. Deshpande *et al* 504–509
  The chronically mentally ill in community facilities: a study of quality of life. C. J. Simpson *et al* 77–82
  The natural history of mental disorder in old age: a long-term study. John R. Robinson 783–789
  Treatment of severe psychiatric illness in a day hospital. Francis Creed *et al* 341–347
  Viruses, immunity and mental disorder. David J. King and Stephen J. Cooper (*Annotation*) 1–7
Psychiatrists.
  Predicting the productive research psychiatrist. Gordon Parker (BR) 109–112
  Referrals from general practitioners to psychiatrists and paramedical mental health professionals. Greg Wilkinson 72–76
Psychiatry.
  1. Psychiatric justice. Thomas Szasz (*Point of view*) 864–869
  2. Szasz on psychiatric justice. D. J. West (*Point of view*) 870–871
  Family therapy influences on general adult psychiatry. David Cottrell 473–477
  The involvement of Soviet psychiatry in the persecution of dissenters. (*Lecture*) 336–340
Psychoanalysis. *A Critical Dictionary of Psychoanalysis*: Charles Rycroft. (John Birtchnell, *Books reconsidered*) 734–737
Psychological-mindedness. Psychological-mindedness and the alexithymia construct. Graeme Taylor *et al* (C) 731–732
Psychopathology. Unsubstantiated complaints of being poisoned. Psychopathology of patients being referred to the National Poisons Unit. E. A. Hutchesson and G. N. Volans 34–40
Psychoses.
  Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function. R. Hunter *et al* 790–796
  Comments on the Northwick Park 'functional' psychosis study. G. M. Goodwin *et al* (*Current literature*) 406–409
  Concomitant treatment of neuroleptic malignant syndrome and psychosis. Harry D. Goldwasser *et al* (BR) 102–104
  CPK levels and neuroleptic malignant syndrome. Hari D. Maharajh (C) 885–886
  Psychotic illness following termination of pregnancy. Kim Davidson and Anthony W. Clare (BR) 559–560
  Sex chromosomes and psychosis. R. S. Shiwach and M. Crocker (C) 722–723, T. J. Crow (C) 723–724
  The classification of functional psychoses and its implications for prognosis. H. J. Möller *et al* 467–472
  The impact of molecular genetics on our understanding of the psychoses. Michael J. Mullan and Robin M. Murray (*Review article*) 591–595
Psychosocial status. Psychosocial status of 192 out-patients with HIV infection and AIDS. Michael B. King 237–242
Psychosurgery. What's so special about two years anyway? Paul Bridges (C) 884–885
Psychotherapy.
  A Study of Brief Psychotherapy: D. H. Malan (Jeremy Holmes, *Books reconsidered*) 891–893
  An uncontrolled study of cognitive therapy for morbid jealousy. N. R. Bishay *et al* 386–389
  Psychotherapy and general practice. Linda Gask and Graeme McGrath (*Review article*) 445–453
  Reflections on psychotherapy with ageing people, individually and in groups. A. Joan G. Hunter (*Point of view*) 250–252
  Self-cathexis and other-cathexis: vicissitudes in the history of an observation. D. Macdiarmid 844–852

Supportive analytical psychotherapy. Sophia Hartland (C) 122–123
The question of therapists' differential effectiveness; a Sheffield Psychotherapy Project addendum. David A. Shapiro *et al* 383–385

Quality of life.
Chronic patients in acute wards. P. M. Abbott *et al* (C) 730
The chronically mentally ill in community facilities: a study of quality of life. C. J. Simpson *et al* 77–82
Questionnaire. The fear questionnaire. W. A. Arrindell (C) 725–726, Florence J. van Zuuren (C) 726–727

Rating scales.
see also **Questionnaire** and **Survey Psychiatric Assessment Schedule**
A rating scale for drug-induced akathisia. Thomas R. E. Barnes 672–676
The use of rating scales to identify post-natal depression. Brian Harris *et al* 813–817
Reading about ... The split-brain syndrome. A. S. David 422–425
Recency theory. Schizophrenia: recency theory and syphilis. Femi Oyebode (C) 269
Rehabilitation. The Glasgow rehabilitation survey. Martin G. Livingston and Adam Bryson 620–624
Relatives' groups. A trial of family therapy v. a relatives group for schizophrenia. J. Leff *et al* 58–66
Research. Predicting the productive research psychiatrist. Gordon Parker (BR) 109–112
Respiratory control. Respiratory control: its contribution to the treatment of panic attacks: a controlled study. George A. Hibbert and Michael Chan 232–236
Review articles.
Affective disorders and cerebral vascular disease. Sergio E. Starkstein and Robert G. Robinson 170–182
Bipolar affective disorder: causes and prevention of relapse. Trevor Silverstone and Sarah Romans-Clarkson 321–335
Day-hospital and community treatment for acute psychiatric illness: a critical appraisal. Francis Creed *et al* 300–310
Dementia and Parkinson's disease. W. R. G. Gibb 596–614
Genetics, Alzheimer's disease and senile dementia. D. W. K. Kay 311–320
Prevention of cardiovascular disease by psychological methods. Derek W. Johnston 183–194
Psychotherapy and general practice. Linda Gask and Graeme McGrath 445–453
Seclusion. Adrian Angold 437–444
The Gilles de la Tourette syndrome: the current status. Mary M. Robertson 147–169
The impact of molecular genetics on our understanding of the psychoses. Michael J. Mullan and Robin M. Murray 591–595
Which depressed patients will respond to electroconvulsive therapy? The search for biological predictors of recovery. Allan F. Scott 8–17
Ryecroft, Charles. *A Critical Dictionary of Psychoanalysis.* (John Birtchnell, *Books reconsidered*) 734–737

S-adenosyl methionine (SAM). The switch mechanism and the bipolar/unipolar dichotomy. M. W. P. Carney *et al* 48–51
Sample size. Sample size and CT scans in schizophrenia. S. W. Lewis (C) 268–269
Schizoaffective disorders.
A family study of two subgroups of schizoaffective patients. Mario Maj 640–643
A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms. David Dodwell and David Goldberg 635–639
Schizophrenia.
A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms. David Dodwell and David Goldberg 635–639
A trial of family therapy v. a relatives' group for schizophrenia. J. Leff *et al* 58–66
Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana. Rajiv Tandon *et al* (BR) 712–714
Community management of schizophrenia: a two-year follow-up of a behavioural intervention with families. Nicholas Tarrier *et al* 625–628
CT studies of schizophrenia. C. Mundt (C) 413
Ethnic density and schizophrenia. Roland Littlewood (C) 123
Factors associated with the course and outcome of schizophrenia in India: results of a two-year multicentre follow-up study. A. Verghese *et al* 499–503
Family history and cerebral ventricular enlargement in schizophrenia: a case control study. Michael J. Owen *et al* 629–634
Internal monitor defect in schizophrenia. T. W. Fan (C) 570–571
Negative and depressive symptoms in schizophrenia. P. Kulhara *et al* 207–211
Positive symptoms of schizophrenia. Howard Ring (C) 268, Brian R. Timney (C) 268, Chris Frith and John Done (C) 569–570
Poverty of speech in schizophrenia and depression during in-patient and post-hospital periods. Ann Barnett Ragin *et al* 52–57
Sample size and CT scans in schizophrenia. S. W. Lewis (C) 268–269
Schizophrenia: recency theory and syphilis. Femi Oyebode (C) 269
Schizophrenia before 1800. J. Foerstl (C) 411–412, Peter K. Carpenter (C) 412
Scottish first episode schizophrenia study. VI. Computerised tomography brain scans in patients and controls. Scottish schizophrenia research group 492–498

- Self-cathexis and other-cathexis: vicissitudes in the history of an observation. D. Macdiarmid 844–852
- Sight and insight: brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography. John L. Waddington (*Annotation*) 433–436
- Suicide among Chinese schizophrenics in Hong Kong. K. K. Cheng *et al* 243–246
- Tactile extinction phenomenon in schizophrenia. O. Gambini *et al* (C) 269–270
- The initial onset of schizophrenia and family expressed emotion: some methodological considerations. Lois Imber Mintz *et al* 212–217
- The nature and prevalence of depression in chronic schizophrenic in-patients. Thomas R. E. Barnes *et al* 486–491
- Unitary models of schizophrenia. C. W. Lo (C) 414–415, Frances Klemperer (C) 415–416, Sue Adams (C) 416–418

Scotland.
- Delusional depression in 19th-century Scotland. Andrew Robinson (C) 573–574
- Scottish first episode schizophrenia study. VI. Computerised tomography brain scans in patients and controls. Scottish schizophrenia research group 492–498

Seclusion. Seclusion. Adrian Angold (*Review article*) 437–444

Self-harm. Depression in self-harm patients. Jon Ennis *et al* 41–47

Self-poisoning. Life events and hostility in self-poisoning. Roger Farmer and Francis Creed 390–395

Self-rating. Self-rating. John S. Price (C) 418

Sex chromosomes. Sex chromosomes and psychosis. R. S. Shiwach and M. Crocker (C) 722–723, T. J. Crop (C) 723–724

Sex differences. Sex differences in the differentiation of psychiatric symptomatology. M. E. Briscoe *et al* 364–367

Sex offences. Castration and the sexual offender. C. J. Hansen and J. Schioldann-Nielsen (C) 272

Sheffield Psychotherapy Project. The question of therapists' differential effectiveness: a Sheffield Psychotherapy Project addendum. David A. Shapiro *et al* 383–385

Shoplifting.
- Loss and theft. R. S. Gillen (C) 721
- Shoplifting in families of mentally handicapped persons. Meera Roy (C) 574

Sleep disorders. Violence in sleep: a further diagnostic consideration. Rachel L. Morehouse (C) 729–730

Social support. Social support and the outcome of major depression. Linda K. George *et al* 478–485

Sorcery. 'Bhanamati' sorcery and psychopathology in South India: a clinical study. M. S. Keshavan *et al* 218–220

Soviet psychiatry. The involvement of Soviet psychiatry in the persecution of dissenters. Anatoly Koryagin (*Lecture*) 336–340

Speech. Poverty of speech in schizophrenia and depression during in-patient and post-hospital periods. Ann Barnett Ragin *et al* 52–57

Spinal cord injury. Depression following spinal cord injury: a prospective in-patient study. Fiona K. Judd *et al* 668–671

Split-brain syndrome. A. S. David (*Reading about* ...) 422–425

Still birth. Lithium in pregnancy and still birth: a case report. S. K. Khandelwal *et al* (BR) 114–116

Stupor.
- Prepubertal depressive stupor. Lorne E. Warneke (C) 418–419
- Teenage depressive stupor. Fuad Hassanyeh and Kenneth Davison (C) 567

Stuttering. Prediction of outcome after treatment for stuttering. Patrick Finn and Merrilyn Gow (C) 273–274

Subacute sclerosing encephalitis (SSPE). Suspected SSPE – a delayed psychiatric presentation. Peter J. B. Mattinson (BR) 116–118

Suicide.
- Hospital suicides: are there preventable factors? Profile of the psychiatric hospital suicide. Sang Eng Goh *et al* 247–249
- Hospital suicides. Marcellino Smyth and Nick Craddock (C) 728, Robert Kehoe (C) 728–729
- Suicide among Chinese schizophrenics in Hong Kong. K. K. Cheng *et al* 243–246
- Treatment of suicidal manic depression. Hameen Markar (C) 123–124

Suicide attempts. *see* **Parasuicide**

Sulphatoxymelatonin. Melatonin and sulphatoxymelatonin in eating disorder patients. S. H. Kennedy *et al* (C) 272–273

Survey Psychiatric Assessment Schedule. Before Mrs Thatcher? N. M. J. Kennedy and D. Gaspar (C) 275

Switch mechanism.
- Affective 'switch mechanisms'. Mamoun Mobayed (C) 884
- The switch mechanism and the bipolar/unipolar dichotomy. M. W. P. Carney *et al* 48–51

Symptoms.
- Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone. Siobhan M. Murphy *et al* 529–534
- Frequency of symptoms in melancholia (depressive illness). M. Hamilton 201–206
- Negative and depressive symptoms in schizophrenia. P. Kulhara *et al* 207–211
- Nosological problems. C. G. Ballard (C) 730
- Positive symptoms of schizophrenia. Howard Ring (C) 268, Brian R. Timney (C) 268, Chris Frith and John Done (C) 569–570
- Sex differences in the differentiation of psychiatric symptomatology. M. E. Briscoe *et al* 364–367

Syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hyponatraemia and clomipramine therapy. D. R. Pledger and H. Mathew (BR) 263–264

Syphilis. Schizophrenia: recency theory and syphilis. Femi Oyebode (C) 269

Tactile extinction. Tactile extinction phenomenon in schizophrenia. O. Gambini *et al* (C) 269–270

Tardive dyskinesia (TD).

Spastic dysphonia and denervation signs in a young man with tardive dyskinesia. Jeffrey A. Lieberman and Ross Reife (BR) 105–109

The course of tardive dyskinesia in patients on long-term neuroleptics. J. A. Bergen *et al* 523–528

Tea. Tea and antipsychotics. John Collier (C) 276

Temperament. Significance of extreme temperament in infancy for clinical status in pre-school years.

I: Value of extreme temperament at 4–8 months for predicting diagnosis at 4.7 years. Michel Maziade *et al* 535–543

II: Patterns of temperament change and implications for the appearance of disorders. Michel Maziade *et al* 544–551

Thatcher, Margaret. Before Mrs Thatcher? N. M. J. Kennedy and D. Gaspar (C) 275

Thioridazine. Concomitant treatment of neuroleptic malignant syndrome and psychosis. Harry D. Goldwasser *et al* (BR) 102–104

Thyroid releasing hormone (TRH) test. The DST and TRH test in bulimia nervosa. A. S. Kaplan *et al* 86–92

Time. As the years go rolling by. Drinking problems in the time dimension. Griffith Edwards (*Benno Pollak lecture 1988*) 18–26

Training. Philosophy for trainees. C. Cabrera-Abreu (C) 575–576

Tranquillisers, minor. Severity of withdrawal in subjects exposed to a combination of alcohol and minor tranquillisers. Christopher S. Thomas *et al* 83–85

Treatment. 'Biological' treatment. E. D. Myers (C) 120–121

Tricyclics. Tricyclic wash-out and growth hormone response to clonidine. M. Schittecatte *et al* 858–863

Uterus. The womb lay still in ancient Egypt. Harold Mersky and Paul Potter (*Comment*) 751–753

Violence.

Lipid-lowering drugs. Ian McLoughlin and Philip Clarke (C) 275–276

Lipid-lowering drugs and violence. David F. Horrobin (C) 882–883

Violence in sleep: a further diagnostic consideration. Rachel L. Morehouse (C) 729–730

Violent incidents in special hospitals. J. B. Coldwell and L. J. Naismith (C) 270

Viruses. Viruses, immunity and mental disorder. David J. King and Stephen J. Cooper (*Annotation*) 1–7

Wards, acute.

Chronic patients in acute wards. P. M. Abbott *et al* (C) 730

The chronically mentally ill in community facilities: a study of quality of life. C. J. Simpson *et al* 77–82

Water intoxication. Altered state of consciousness in a compulsive water drinker. Sing Lee *et al* (BR) 556–558

Wernicke's encephalopathy. Wernicke's encephalopathy in an 18-year-old woman. Stuart Turner *et al* (BR) 261–262

Womb. The womb lay still in ancient Egypt. Harold Mersky and Paul Potter (*Comment*) 751–753

Women.

Parasuicide in young Asian women. Gyles Glover *et al* (C) 271–272

Women who kill their parents. P. T. d'Orban and Art O'Connor 27–33

Zuclopenthixol. Zuclopenthixol-induced neuroleptic malignant syndrome at rechallenge and its extrapyramidal effects. Charles J. F. Kemperman (BR) 562–563

PART II. CONTRIBUTORS

Abas, Melanie *see* **Fahy, Thomas A.** *et al* (BR) 99–101

Abbott, P. M. *et al.* Chronic patients in acute wards (C) 730

Adams, Sue. Unitary models of schizophrenia (C) 416–418

Alexandra, Heather *see* **Caplan, H. L.** *et al* 818–822

Allderidge, Patricia H. *see* **Persaud, Rajendra D.** (C) 719–720

Allsopp, M. and **Verduyn, C.** A follow-up of adolescents with obsessive–compulsive disorder 829–834

Anderson, D. N. A comparison of in-patient and out-patient prescribing 644–649

Angold, Adrian. Seclusion (*Review article*) 437–444

Anthony, Philip *see* **Creed, Francis** *et al* 341–347

Anthony, Philip *see* **Creed, Francis** (*Review article*) 300–310

Appleby, Louis *et al.* The psychiatrist in the obstetric unit: establishing a liaison service 510–515

Arrindell, W. A. The fear questionnaire (C) 725–726

Avasthi, A. *see* **Kulhara, P.** *et al* 207–211

Bagby, Michael *see* **Taylor, Graeme** *et al* (C) 731–732

Balestrieri, Matteo *see* **Williams, Paul** 67–71

Ball, Christopher and **Exworthy, Tim.** Capgras' syndrome and town duplication (C) 889–890

Ballard C. G. ECT mythology? (C) 575

Ballard C. G. Nosological problems (C) 730

Bamrah, J. S. *see* **Tarrier, Nicholas** *et al* 625–628

Barnes, Rosemary A. *see* **Ennis, Jon** *et al* 41–47

Barnes, Thomas R. E. A rating scale for drug-induced akathisia 672–676

Barnes, Thomas R. E. *et al.* The nature and prevalence of depression in chronic schizophrenic in-patients 486–491

Barrett, Ken. Manic features during a course of ECT (C) 575
Barrowclough, Christine *see* **Tarrier, Nicholas** *et al* 625–628
Barry, Siobhan *see* **Yatham, Lakshmi N.** *et al* (C) 879
Basoglu, Metin *see* **Marks, Mark** (C) 565–567
Beats, Barbara *see* **Howells, Roger** (*Case conference*) 872–876
Beaumont, George. The toxicity of antidepressants (*Comment*) 454–458
Bebbington, Paul *see* **McGuffin, Peter** *et al* (C) 565
Bellini, L. *see* **Gambini, O.** *et al* (C) 269–270
Benjamin, Jonathan. The mind–body problem (C) 731
Bentley, J. *see* **Abbott, P. M.** *et al* (C) 730
Bergen, J. A. *et al.* The course of tardive dyskinesia in patients on long-term neuroleptics 523–528
Berkowitz, R. *see* **Leff, J.** *et al* 58–66
Bernardi, Elsa *et al.* Quality of parenting in alcoholics and narcotic addicts 677–682
Bernier, Hugues *see* **Maziade, Michel** *et al* 535–543, 544–551
Best, J. J. K. *see* **Scottish Schizophrenia Research Group** *et al* 492–498
Beumont, P. J. V. *see* **Bergen, J. A.** *et al* 523–528
Bird, Jeremy *see* **Mace, Chris** (C) 727
Birleson, Peter. Childhood and adolescent depression (C) 267–268
Birtchnell, John. *A Critical Dictionary of Psychoanalysis*: Charles Rycroft (*Books reconsidered*) 734–737
Bishay, N. R. *et al.* An uncontrolled study of cognitive therapy for morbid jealousy 386–389
Black, Dawn *see* **Creed, Francis** (*Review article*) 300–310
Blazer, Dan G. *see* **George, Linda K.** *et al* 478–485
Blazer, Dan G. *see* **Tweed, J. Lindsey** *et al* 823–828
Boon, Suzette *see* **Hart, Onno van der** (C) 419
Bottiglieri, T. *see* **Carney, M. W. P.** *et al* 48–51
Boutin, Pierrette *see* **Maziade, Michel** *et al* 535–543, 544–551
Bradley, Brendan P. *et al.* Circumstances surrounding the initial lapse to opiate use following detoxification 354–359
Bradley, Brendan *see* **Gossop, Michael** *et al* 348–353, 360–363
Brewer, Colin. Naltrexone and clonidine in heroin withdrawal treatment (C) 572
Bridges, Paul. What's so special about two years anyway? (C) 884–885
Briscoe, M. E. *et al.* Sex differences in the differentiation of psychiatric symptomatology 364–367
Bristow, M. F. Molecular genetics and ethics (C) 882
Brown, Douglas J. *see* **Judd, Fiona K.** *et al* 668–671
Brown, G. M. *see* **Kaplan, A. S.** *et al* 86–92
Brown, G. M. *see* **Kennedy, S. H.** *et al* (C) 272–273
Brown, Jeremy Christie *see* **Fahy, Thomas A.** *et al* (BR) 99–101
Bryson, Adam *see* **Livingston, Martin G.** 620–624
Burrows, Graham D. *see* **Judd, Fiona K.** *et al* 668–671

Cabrera-Abreu, C. Philosophy for trainees (C) 575–576
Campbell, J. A. *see* **Bergen, J. A.** *et al* 523–528
Caplan, H. L. *et al.* Maternal depression and the emotional development of the child 818–822
Carney, M. W. P. *et al.* The switch mechanism and the bipolar/unipolar dichotomy 48–51
Carpenter, Peter K. and **King, Alan L.** Epilepsy and arson (BR) 554–556
Carpenter, Peter K. Schizophrenia before 1800 (C) 412
Casey, Patricia *see* **Kreitman, Norman** (C) 721
Chadda, R. *see* **Kulhara, P.** *et al* 207–211
Chan, Michael *see* **Hibbert, George A.** 232–236
Chandiramani, K. *see* **Kulhara, P.** *et al* 207–211
Charles, D. *see* **Schittecatte, M.** *et al* 858–863
Chary, T. K. N. *see* **Carney, M. W. P.** *et al* 48–51
Chaturvedi, Santosh K. Delusions of pregnancy in men: case report and review of the literature (BR) 716–718
Chen, Char-Nie *see* **Lee, Sing** *et al* 683–688
Cheng, K. K. *et al* Suicide among Chinese schizophrenics in Hong Kong 243–246
Chiu, Helen F. K. *see* **Lee, Sing** *et al* 683–688
Choi, Precilla and **Parrott, Andrew.** Illicit drug use in strength athletes (C) 732–733
Chow, Chun Chung *see* **Lee, Sing** *et al* (BR) 556–558
Christie, J. E. *see* **Hunter, R.** *et al* 790–796
Clare, Anthony W. *see* **Davidson, Kim** (BR) 559–560
Clarke, Philip *see* **McLoughlin, Ian** (C) 275–276
Cogill, S. R. *see* **Caplan, H. L.** *et al* 818–822
Cohen, Samuel I. Hyperventilation causing asthma (C) 576–577
Coldwell, J. B. and **Naismith, L. J.** Violent incidents in special hospitals (C) 270
Collier, John. Tea and antipsychotics (C) 276
Connelly, J. B. HIV screening (C) 266–267
Cookson, I. B. *see* **Abbott, P. M.** *et al* (C) 730
Cooper, Peter J. *see* **Cooper, Zafra** *et al* 807–812
Cooper, Stephen J. *see* **King, David J.** (*Annotation*) 1–7
Cooper, Zafra *et al.* The validity of the eating disorder examination and its subscales. Zaffra Cooper *et al* 807–812
Cording-Tommel, C. *see* **Moller, H. J.** *et al* 467–472
Côté, Robert *see* **Maziade, Michel** *et al* 535–543, 544–551
Cottrell, David. Family therapy influences on general adult psychiatry 473–477
Craddock, Nick *see* **Smyth, Marcellino** (C) 728
Craig, T. K. J. and **Murphy, Elaine.** Camberwell collaborative depression study (C) 564–565
Creed, Francis *et al.* Day-hospital and community treatment for acute psychiatric illness: a critical appraisal (*Review article*) 300–310
Creed, Francis *et al.* Treatment of severe psychiatric illness in a day hospital 341–347
Creed, Francis *see* **Farmer, Roger** 390–395
Crocker, M. *see* **Shiwach, R. S.** (C) 722–723
Crombie, W. *see* **McCreadie, R. G.** *et al* 229–231
Crow, T. J. Sex chromosomes and psychosis (C) 723–724
Curzon, David A. *see* **Barnes, Thomas R. E.** *et al* 486–491

Daniel, Walter F. *et al* Conversion disorders and ECT (C) 274–275
Daniels, Lynn *see* **Turner, Stuart** (BR) 261–262

David, A. S. Split-brain syndrome (*Reading about …*) 422–425

David, Anthony S. Molecular genetics and human disease (C) 119

Davidson, Kim and **Clare, Anthony W.** Psychotic illness following termination of pregnancy (BR) 559–560

Davison, Kenneth *see* **Hassanyeh, Fuad** (C) 567

Deahl, Martin *see* **Mace, Chris** (C) 727

Deary, I. J. and **Wilson, Janet A.** Is globus hystericus? (C) 727–728

Dennerstein, Lorraine *see* **Ryan, Margaret M.** *et al* 516–522

Deshpande, S. N. *et al.* Psychiatric disorders among medical in-patients in an Indian hospital 504–509

Dewsnap, Paul-Allan and **Stein, George.** Non-psychotic psychiatric disorder after childbirth (C) 119–120

Diez-Manrique, J. F. *see* **Briscoe, M. E.** *et al* 364–367

Dinan, Timothy G. *see* **Yatham, Lakshmi N.** *et al* (C) 879

Dodwell, David and **Goldberg, David.** A study of factors associated with response to electroconvulsive therapy in patients with schizophrenic symptoms 635–639

Dolan, Ray *see* **Mace, Chris** (C) 727

Done, John *see* **Frith, Chris** (C) 569–570

Donnelly, Patricia *see* **McClune, Noel** (C) 889

d'Orban, P. T. and **O'Connor, Art.** Women who kill their parents 27–33

Drummond, D. Colin and **Turkington, Douglas.** Naltrexone and clonidine in heroin withdrawal treatment (C) 571–572

Duncan, Janice M. Listeria and psychiatric syndromes (C) 887

Dutchak, Denise *see* **Tandon, Rajiv** (BR) 712–714

Dykes, Sheena *see* **Scott, Allan I. F.** 853–857

Eastwood, M. R. *et al.* Mood disorder following cerebrovascular accident 195–200

Edwards, Griffith. As the years go rolling by. Drinking problems in the time dimension (*Benno Pollak lecture 1988*) 18–26

Eisenberg, Leon. Health education and the AIDS epidemic 754–767

Ennis, Jon *et al.* Depression in self-harm patients 41–47

Evans, C. Psychiatrists' responses to personality disorder (C) 265–266

Exworthy, Tim *see* **Ball, Christopher** (C) 889–890

Eyland, E. A. *see* **Bergen, J. A.** *et al* 523–528

Fahy, Thomas A. *et al.* Multiple personality: a symptom of psychiatric disorder (BR) 99–101

Fahy, Tom. Multiple personality disorder (C) 878

Fairburn, Christopher G. *see* **Cooper, Zafra** *et al* 807–812

Fairburn, Christopher G. *see* **Morris, Charles H.** *et al* 801–806

Fan, T. W. Internal monitor defect in schizophrenia (C) 570–571

Faragher, E. B. *see* **Simpson, C. J.** *et al* 77–82

Farmer, Roger and **Creed, Francis.** Life events and hostility in self-poisoning 390–395

Feinstein, Anthony *see* **Mace, Chris** (C) 727

Ferrington, C. *see* **Hunter, R.** *et al* 790–796

Finn, Patrick and **Gow, Merrilyn.** Prediction of outcome after treatment for stuttering (C) 273–274

Firth-Cozens, Jenny *see* **Shapiro, David A.** *et al* 383–385

Fisch, Robert Z. Alexithymia, masked depression and loss in a holocaust survivor (BR) 708–710

Fleming, Jonathan A. E. Multiple personality disorder (C) 877

Foerstl, J. Schizophrenia before 1800 (C) 411–412

Fowler, Nancy *see* **George, Linda K.** *et al* 478–485

Fox, Helena *see* **Appleby, Louis** *et al* 510–515

Freeman, Hugh (*Editor, British Journal of Psychiatry*). Journal supplements (C) 121

Freeman, Hugh *see* **Tarrier, Nicholas** *et al* 625–628

Frith, Chris and **Done, John.** Positive symptoms of schizophrenia (C) 569–570

Fukushima, Yutaka *see* **Otani, Koichi** *et al* (BR) 113–114

Fung, Hedi *see* **Harris, Brian** *et al* 660–667, 813–817

Gaddal, Y. Y. El. De Clérambault's syndrome (erotomania) in organic delusional syndrome (BR) 714–716

Gambini, O. *et al* Tactile extinction phenomenon in schizophrenia (C) 269–270

Gangadhar, B. N. *see* **Keshavan, M. S.** *et al* 218–220

Garfinkel, P. E. *see* **Kaplan, A. S.** *et al* 86–92

Garfinkel, P. E. *see* **Kennedy, S. H.** *et al* (C) 272–273

Gask, Linda and **McGrath, Graeme.** Psychotherapy and general practice (*Review article*) 445–453

Gaspar, D. *see* **Kennedy, N. M. J.** (C) 275

Gath, Ann. *Child Care and the Growth of Love*: John Bowlby (*Books reconsidered*) 579–580

George, Linda K. *et al* Social support and the outcome of major depression 478–485

George, Linda K. *see* **Tweed, J. Lindsey** *et al* 823–828

Ghodse, A. H. *see* **London, M.** 835–838

Gibb, W. R. G. Dementia and Parkinson's disease. (*Review article*) 596–614

Gilhooly, G. *see* **McCreadie, R. G.** *et al* 229–231

Gillen, R. S. Loss and theft (C) 721

Glass, I. *see* **Leff, J.** *et al* 58–66

Glover, Gyles *et al.* Parasuicide in young Asian women (C) 271–272

Glue, Paul *see* **Nutt, David** (*Annotation*) 287–291

Godbert, Ken *see* **Creed, Francis** *et al* 341–347

Goh, Seng Eng *et al.* Hospital suicides: are there preventable factors? Profile of the psychiatric hospital suicide 247–249

Goldberg, David *see* **Dodwell, David** 635–639

Goldney, Robert D. Depression in attempted suicide (C) 881–882

Goldstein, Michael J. *see* **Mintz, Lois Imber** *et al* 212–217

Goldwasser, Harry D. *et al.* Concomitant treatment of neuroleptic malignant syndrome and psychosis (BR) 102–104

Goodman, Robert. Neuronal misconnections and psychiatric disorder: is there a link? (*Comment*) 292–299

Goodwin, G. M. *et al.* Comments on the Northwick Park 'functional' psychosis study (*Current literature*) 406–409

Goodwin, G. M. *see* **Hunter, R.** *et al* 790–796
Goss, W. H. History of depressive disorder (C) 122
Gossop, Michael *et al.* Lapse, relapse and survival among opiate addicts after treatment: a prospective follow-up study 348–353
Gossop, Michael *see* **Bradley, Brendan P.** *et al* 354–359
Gow, Merrilyn *see* **Finn, Patrick** (C) 273–274
Gray, Jeffrey *see* **Sahakian, Barbara** *et al* 797–800
Greden, John F. *see* **Tandon, Rajiv** (BR) 712–714
Green, B. H. Capgras' syndrome (C) 271
Green, Benjamin Hugh. Neuroleptic malignant syndrome and pneumomediastinum (BR) 560–561
Green, Lynette *see* **Bradley, Brendan P.** *et al* 354–359
Green, Lynette *see* **Gossop, Michael** *et al* 348–353
Greene, Sheila M. The relationship between depression and hopelessness: implications for current theories of depression 650–659
Greer, Steven *see* **Turner, Stuart** (BR) 261–262
Griffiths, Paul *see* **Gossop, Michael** *et al* 360–363
Grohmann, R. *see* **Schmidt, L. G.** *et al* 839–843

Hackett, Richard D. *see* **Thomas, Christopher S.** *et al* 83–85
Hambridge, D. M. Photography for anorexia nervosa (C) 575
Hamilton, M. Frequency of symptoms in melancholia (depressive illness) 201–206
Hansen, C. J. and **Schioldann-Nielsen, J.** Castration and the sexual offender (C) 272
Harper, Rod *see* **Kuipers, Liz** *et al* 775–782
Harper, Rod *see* **MacCarthy, Brigid** *et al* 768–775
Harris, Brian *et al.* The hormonal environment of post-natal depression 660–667
Harris, Brian *et al.* The use of rating scales to identify post-natal depression 813–817
Harris, S. J. *see* **Wylie, K. R.** *et al* (C) 419–420
Harrison, Judy. 'Good old days' of psychiatry (C) 126
Harrop, F. M. *see* **Wylie, K. R.** *et al* (C) 419–420
Hart, J. and **McClure, G. M. G.** Capgras' syndrome and folie à deux involving mother and child (BR) 552–554
Hart, Onno van der *and* **Boon, Suzette.** Multiple personality disorder (C) 419
Hartland, Sophia. Supportive analytical psychotherapy (C) 122–123
Hassanyeh, Fuad and **Davison, Kenneth.** Teenage depressive stupor (C) 567
Hibbert, George A. and **Chan, Michael.** Respiratory control: its contribution to the treatment of panic attacks. A controlled study 232–236
Hill, R. F. The opiate prescribing debate (C) 888–889
Hobe-Schramm, M. *see* **Moller, H. J.** *et al* 467–472
Holden, T. J. Defining personality disorder (C) 567–568
Holmes, Jeremy. *A Study of Brief Psychotherapy*: D. H. Malan (*Books reconsidered*) 891–893
Hooper, James F. *see* **Goldwasser, Harry D.** *et al* (BR) 102–104
Hope, R. A. *see* **Morris, Charles H.** *et al* 801–806
Hore, Brian D. *see* **Thomas, Christopher S.** *et al* 83–85
Horrobin, David F. Lipid-lowering drugs and violence (C) 882–883
Hosty, Gary. Admission trends (C) 731
Howells, Roger and **Beats, Barbara.** A dementia syndrome of dependency (*Case conference*) 872–876
Huckle, Philip *see* **Harris, Brian** *et al* 813–817
Hughes, Dana C. *see* **George, Linda K.** *et al* 478–485
Hunter, A. Joan G. Reflections on psychotherapy with ageing people, individually and in groups (*Point of view*) 250–252
Hunter, R. *et al.* Cerebral vascular transit time in Alzheimer's disease and Korsakoff's psychosis and its relation to cognitive function 790–796
Hurry, Jane *see* **Kuipers, Liz** *et al* 775–782
Hurry, Jane *see* **MacCarthy, Brigid** *et al* 768–775
Hutchesson, E. A. and **Volans, N.** Unsubstantiated complaints of being poisoned: psychopathology of patients being referred to the National Poisons Unit 34–40
Huws, Rhodri. Benzodiazepine addiction in heroin addicts (C) 886
Huxley, Peter *see* **Creed, Francis** *et al* 341–347
Hyde, C. E. *see* **Simpson, C. J.** *et al* 77–82

Jansen, Karl L. R. The near-death experience (C) 883–884
Jelley, Matt. Journal supplements (C) 121
Jenkings, R. *see* **Bergen, J. A.** *et al* 523–528
John, J. K. *see* **Verghese, A.** *et al* 499–503
Johns, Sandra *see* **Harris, Brian** *et al* 660–667, 813–817
Johnson, D. A. W. *see* **Goodwin, G. M.** (*Current literature*) 406–409
Johnston, Derek W. Prevention of cardiovascular disease by psychological methods (*Review article*) 183–194
Jones, Erica M. EEG monitoring of ECT (C) 880–881
Jones, Gemma *see* **Sahakian, Barbara** *et al* 797–800
Jones, Michael *see* **Bernardi, Elsa** *et al* 677–682
Joseph, S. *see* **Kulhara, P.** *et al* 207–211
Joyce, Eileen M. and **Levy, Raymond** Treatment of mood disorder associated with Binswanger's disease (BR) 259–261
Judd, Fiona K. *et al* Depression following spinal cord injury: a prospective in-patient study 668–671

Kamlana, S. H. Lithium-induced paranoid hallucinatory state (C) 273
Kaneko, Suano *see* **Otani, Koichi** *et al* (BR) 113–114
Kaplan, A. S. *et al* The DST and TRH test in bulimia nervosa 86–92
Katz, Randy *see* **McGuffin, Peter** *et al* (C) 565
Kay, D. W. K. Genetics, Alzheimer's disease and senile dementia (*Review article*) 311–320
Kay, D. W. K. Prevalence of dementia (C) 121–122
Kehoe, Robert. Hospital suicides (C) 728–729
Kehoe, Robert *see* **Young, Robert** (BR) 710–712
Kellehear, K. *see* **Bergen, J. A.** *et al* 523–528
Kemperman, Charles J. F. Zuclopenthixol-induced neuroleptic malignant syndrome at rechallenge and its extrapyramidal effects (BR) 562–563

Kennedy, N. M. J. and **Gaspar, D.** Before Mrs Thatcher? (C) 275
Kennedy, S. H. *et al.* Melatonin and sulphatoxymelatonin in eating disorder patients (C) 272–273
Kennedy, Sydney *see* **Ennis, Jon** *et al* 41–47
Keshavan, M. S. *et al.* 'Bhanamati' sorcery and psychopathology in South India: a clinical study 218–220
Khandelwal, S. K. *et al.* Lithium in pregnancy and still birth: a case report (BR) 114–116
King, Alan L. *see* **Carpenter, Peter K.** (BR) 554–556
King, David J. and **Cooper, Stephen J.** Viruses, immunity and mental disorder (*Annotation*) 1–7
King, Michael B. Psychosocial status of 192 out-patients with HIV infection and AIDS 237–242
Klemperer, Frances. Unitary models of schizophrenia (C) 415–416
Koo, Linda C. L. *see* **Lee, Sing** *et al* (BR) 556–558
Koryagin, Anatoly. The involvement of Soviet psychiatry in the persecution of dissenters (*Lecture: Autumn Quarterly Meeting 1987*) 336–340
Kota, S. K. *see* **Kulhara, P.** *et al* 207–211
Kreitman, Norman and **Casey, Patricia.** Repetition of parasuicide (C) 721
Kubota, Shuji *see* **Otani, Koichi** *et al* (BR) 113–114
Kuipers, Liz *et al.* Counselling the relatives of the long-term adult mentally ill: II. A low-cost supportive model 775–782
Kuipers, Liz *see* **MacCarthy, Brigid** *et al* 768–775
Kulhara, P. *et al.* Negative and depressive symptoms in schizophrenia 207–211
Kumar, R. *see* **Appleby, Louis** *et al* 510–515
Kumar, R. *see* **Caplan, H. L.** *et al* 818–822

Lam, T. H. *see* **Cheng, K. K.** *et al* 243–246
Lee, Sing *et al.* Altered state of consciousness in a compulsive water drinker (BR) 556–558
Lee, Sing *et al.* Anorexia nervosa in Hong Kong: why not more Chinese? 683–688
Leff, J. *et al.* A trial of family therapy v. a relatives' group for schizophrenia 58–66
LeSage, Alain *see* **MacCarthy, Brigid** *et al* 768–775
Leung, C. M. *see* **Cheng, K. K.** *et al* 243–246
Levy, Raymond *see* **Joyce, Eileen M.** (BR) 259–261
Levy, Raymond *see* **Sahakian, Barbara** *et al* 797–800
Lewis, S. W. Sample size and CT scans in schizophrenia (C) 268–269
Lewis, Shon *see* **Owen, Michael J.** *et al* 629–634
Lewis, Shon W. Capgras' syndrome (C) 270–271
Liddle, Peter F. *see* **Barnes, Thomas R. E.** *et al* 486–491
Lieberman, Jeffery A. and **Reife, Ross.** Spastic dysphonia and denervation signs in a young man with tardive dyskinesia (BR) 105–109
Lilienfeld, Scott O. Defining personality disorder (C) 568–569
Lipkin, Bron. Capgras' syndrome (C) 414
Littlewood, Roland. Ethnic density and schizophrenia (C) 123
Livingston, Martin G. and **Bryson, Adam.** The Glasgow rehabilitation survey 620–624
Lo, C. W. Unitary models of schizophrenia (C) 414–415
Lo, W. H. *see* **Cheung, K. K.** *et al* 243–246
London, M. and **Ghodse, A. H.** Types of opiate addiction and notification to the Home Office 835–838
Lucas, C. P. *et al.* The occurrence of depression following mania: a method of predicting vulnerable cases (BR) 705–708
Lucas, S. B. *see* **Lucas, C. P.** *et al* (BR) 705–708

MacCarthy, Brigid *et al.* Counselling the relatives of the long-term adult mentally ill: I. Evaluation of the impact on relatives and patients 768–775
MacCarthy, Brigid *see* **Kuipers, Liz** *et al* 775–782
McClune, Noel and **Donnelly, Patricia.** Children surviving parental murder (C) 889
McClure, G. M. G. *see* **Hart, J.** (BR) 552–554
McCreadie, R. G. *see* **Goodwin, G. M.** (*Current literature*) 406–409
McCreadie, R. G. *et al.* Is electroencephalographic monitoring of electroconvulsive therapy clinically useful? 229–231
McCreadie, Robin G. EEG monitoring of ECT (C) 881
Macdiarmid, D. Self-cathexis and other-cathexis: vicissitudes in the history of an observation 844–852
MacDonald, Alistair J. Paradoxical intervention (C) 883
Macdonald, H. L. *see* **Scottish Schizophrenia Research Group** *et al* 492–498
McDonald, J. and **Wafer, K.** Munchausen syndrome masquerading as AIDS-induced depression (C) 420–421
Mace, Chris *et al.* Is globus hystericus? (C) 727
McFarlane, Alexander C. The aetiology of post-traumatic morbidity: predisposing, precipitating and perpetuating factors 221–228
McGrath, Graeme *see* **Gask, Linda** (*Review article*) 445–453
McGuffin, Peter *et al.* The Camberwell collaborative depression study (C) 565
Machowski, R. *see* **Schittecatte, M.** *et al* 858–863
McLoughlin, Ian and **Clarke, Philip.** Lipid-lowering drugs (C) 275–276
McLuskie, R. *see* **Hunter, R.** *et al* 790–796
McMurray, J. *see* **Shrimankar, J.** *et al* 372–377
Maharajh, Hari D. CPK levels and neuroleptic malignant syndrome (C) 885–886
Maj, Mario. A family study of two subgroups of schizoaffective patients 640–643
Markar, Hameen. Treatment of suicidal manic depression (C) 123–124
Marks, Francis *see* **Glover, Gyles** *et al* (C) 271–272
Marks, Isaac and **Basoglu, Metin.** Obsessive–compulsive rituals (C) 565–567
Markus, A. C. *see* **Wilkinson, Greg** 378–382
Mathew, H. *see* **Pledger, D. R.** (BR) 263–264
Mattinson, Peter J. B. Suspected SSPE – a delayed psychiatric presentation (BR) 116–118
Mattoo, S. K. *see* **Kulhara, P.** *et al* 207–211
Maziade, Michel *et al.* Significance of extreme temperament in infancy for clinical status in pre-school years.
  I: Value of extreme temperament at 4–8 months for predicting diagnosis at 4.7 years 535–543

II: Patterns of temperament change and implications for the appearance of disorders 544–551
Merrick, M. V. *see* **Hunter, R.** *et al* 790–796
Merskey, Harold and **Potter, Paul.** The womb lay still in ancient Egypt (*Comment*) 751–753
Milner, G. L. Organic reaction in AIDS (BR) 255–257
Mintz, Jim *see* **Mintz, Lois Imber** *et al* 212–217
Mintz, Lois Imber *et al.* The initial onset of schizophrenia and family expressed emotion: some methodological considerations 212–217
Mobayed, Mamoun. Affective 'switch mechanisms' (C) 884
Möller, H. J. *et al.* The classification of functional psychoses and its implications for prognosis 467–472
Morehouse, Rachel L. Violence in sleep: a further diagnostic consideration (C) 729–730
Morris, Charles H. *et al.* Eating habits in dementia: a descriptive study 801–806
Morris, Michael. Elementary, my dear Freud (C) 412–413
Mullan, Michael J. and **Murray, Robin M.** The impact of molecular genetics on our understanding of the psychoses (*Review article*) 591–595
Müller-Oerlinghausen, B. *see* **Priebe, S.** *et al* 396–399
Müller-Oerlinghausen, B. *see* **Schmidt, L. G.** *et al* 839–843
Mundt, C. CT studies of schizophrenia (C) 413
Murphy, Elaine *see* **Craig, T. K. J.** (C) 564–565
Murphy, Siobhan M. *et al.* Comparative assessment of efficacy and withdrawal symptoms after 6 and 12 weeks' treatment with diazepam or buspirone 529–534
Murray, Robin M. *see* **Mullan, Michael J.** (*Review article*) 591–595
Murray, Robin M. *see* **Owen, Michael J.** *et al* 629–634
Myers, E. D. 'Biological' treatment (C) 120–121

Naismith, L. J. *see* **Coldwell, J. B.** (C) 270
Narayanan, H. S. *see* **Keshavan, M. S.** *et al* 218–220
Nemiah, John. The varieties of human experience (*Adolph Meyer lecture 1988*) 459–466
Newton, J. R. *et al.* Thirty years' war, a battle with insomnia (*Case conference*) 691–696
Nobbs, H. *see* **Eastwood, M. R.** *et al* 195–200
Notghi, A. *see* **Hunter, R.** *et al* 790–796
Nowers, Mike *see* **Glover, Gyles** *et al* (C) 271–272
Nuechterlein, Keith H. *see* **Mintz, Lois Imber** *et al* 212–217
Nutt, David and **Glue, Paul.** Monoamine oxidase inhibitors: rehabilitation from recent research? (*Annotation*) 287–291

O'Connor, Art *see* **d'Orban, P. T.** 27–33
Oltmanns, Thomas F. *see* **Ragin, Ann Barnett** *et al* 52–57
Otani, Koichi *et al.* Involuntary movements associated with mianserin treatment: a case report (BR) 113–114
Otto, M. *see* **Schmidt, L. G.** *et al* 839–843
Owen, Michael J. *et al.* Family history and cerebral ventricular enlargement in schizophrenia: a case control study 629–634
Owen, Robert *see* **Murphy, Siobhan M.** *et al* 529–534
Oyebode, Femi. Schizophrenia: recency theory and syphilis (C) 269

Parker, Gordon. Predicting the productive research psychiatrist (BR) 109–112
Parker, James *see* **Taylor, Graeme** *et al* (C) 731–732
Parrott, Andrew *see* **Choi, Precilla** (C) 732–733
Patel, Meena *see* **Barnes, Thomas R. E.** *et al* 486–491
Peet, Malcolm *see* **Wright, Simon** (BR) 257–259
Pena, C. *see* **Briscoe, M. E.** *et al* 364–367
Pepperell, Roger *see* **Ryan, Margaret M.** *et al* 516–522
Persaud, Rajendra D. and **Allderidge, Patricia H.** Taking a good history (C) 719–720
Petersen, N. *see* **Bishay, N. R.** *et al* 386–389
Phillips, Grania *see* **Bradley, Brendan P.** *et al* 354–359
Phillips, Grania *see* **Gossop, Michael** *et al* 348–353
Phillips, K. *see* **McCreadie, R. G.** *et al* 229–231
Pitt, Brice. Non-psychotic psychiatric disorder after childbirth (C) 119–120
Pledger, D. R. and **Mathew, H.** Hyponatraemia and clomipramine therapy (BR) 263–264
Pogue-Geile, Michael *see* **Ragin, Ann Barnett** *et al* 52–57
Porceddu, Kathleen *see* **Tarrier, Nicholas** *et al* 625–628
Potter, Paul *see* **Mersky, Harold** (*Comment*) 751–753
Powell, C. Elderly eccentrics (C) 724
Price, John S. Self-rating (C) 418
Priebe, S. *et al.* Lithium prophylaxis and expressed emotion (EE) 396–399

Ragin, Ann Barnett *et al.* Poverty of speech in schizophrenia and depression during in-patient and post-hospital periods 52–57
Rajkumar, S. *see* **Verghese, A.** *et al* 499–503
Rands, Gianetta. Failure to convulse with ECT (C) 125
Read, Graham *see* **Harris, Brian** *et al* 660–667
Reder, Peter. Freud's family (*Point of view*) 93–98
Reife, Ross *see* **Leibermann, Jeffrey A.** (BR) 105–109
Reynolds, E. H. *see* **Carney, M. W. P.** *et al* 48–51
Riad-Fahmy, Diana *see* **Harris, Brian** *et al* 660–667
Richard, J. *see* **Verghese, A.** *et al* 499–503
Richards, A. *see* **Bergen, J. A.** *et al* 523–528
Rifat, S. L. *see* **Eastwood, M. R.** *et al* 195–200
Rigby, J. C. *see* **Lucas, C. P.** *et al* (BR) 705–708
Ring, Howard. Positive symptoms of schizophrenia (C) 268
Robertson, Mary M. The Gilles de la Tourette syndrome: the current status (*Review article*) 147–169
Robinson, A. D. T. *see* **McCreadie, R. G.** *et al* 229–231
Robinson, Andrew. Delusional depression in 19th-century Scotland (C) 573–574
Robinson, John R. The natural history of mental disorder in old age, a long-term study 783–789
Robinson, P. H. Perceptivity and paraperceptivity during measurement of gastric emptying in anorexia and bulimia nervosa 400–405

Robinson, Robert G. *see* **Starkstein, Sergio E.** (*Review article*) 170–182

Robson, Kay Mordecai *see* **Caplan, H. L.** *et al* 818–822

Rollin, Henry. Inebriate criminal responsibility (*A hundred years ago*) 276–277

Rollin, Henry. Insomnia (*A hundred years ago*) 890

Rollin, Henry. Medico-Psychological Association. Certificate in Psychological Medicine – examination questions (*A hundred years ago*) 578

Rollin, Henry. Medico-Psychological Association. Quarterly meeting (*A hundred years ago*) 126

Rollin, Henry. The education of idiots and imbeciles (*A hundred years ago*) 733

Romans-Clarkson, Sarah *see* **Silverstone, Trevor** (*Review article*) 321–335

Ron, Maria *see* **Mace, Chris** (C) 727

Roy, Meera. Shoplifting in families of mentally handicapped persons (C) 574

Ruderman, J. *see* **Eastwood, M. R.** *et al* 195–200

Ruther, E. *see* **Schmidt, L. G.** *et al* 839–843

Ryan, Margaret M. *et al.* Psychological aspects of hysterectomy: a prospective study 516–522

Sagar, R. S. *see* **Khandelwal, S. K.** *et al* (BR) 114–116

Sahakian, Barbara *et al.* The effects of nicotine on attention, information processing and short-term memory in patients with dementia of the Alzheimer type 797–800

Salmons, Paula H. *see* **Goh, Seng Eng** *et al* 247–249

Saxena, S. *see* **Khandelwal, S. K.** *et al* (BR) 114–116

Scannell, T. D. Community care and the difficult and offender patient (*Comment*) 615–619

Scarone, S. *see* **Gambini, O.** *et al* (C) 269–270

Schick, Ivan G. Failure to convulse with ECT (C) 125

Schioldann-Nielsen, J. *see* **Hansen, C. J.** (C) 272

Schittecatte, M. *et al.* Tricyclic wash-out and growth hormone response to clonidine 858–863

Schmid-Bode, W. *see* **Moller, H. J.** *et al* 467–472

Schmidt, L. G. *et al.* Prevalence of benzodiazepine abuse and dependence in psychiatric in-patients with different nosology: an assessment of hospital-based drug surveillance data 839–843

Schoenbach, Victor J. *see* **Tweed, J. Lindsey** *et al* 823–828

Scott, Allan *et al.* Which patients will respond to ECT? (C) 879–880

Scott, Allan F. Which depressed patients will respond to electroconvulsive therapy? The search for biological predictors of recovery (*Review article*) 8–17

Scott, Allan I. F. *et al.* Would monitoring by electroencephalogram improve the practice of electroconvulsive therapy? 853–857

Scottish Schizophrenia Research Group *et al.* Scottish first episode schizophrenia study. VI. Computerised tomography brain scans in patients and controls 492–498

Sethi, B. B. *see* **Verghese, A.** *et al* 499–503

Shapiro, C. *see* **Newton, J. R.** *et al* (*Case conference*) 691–696

Shapiro, David A. *et al.* The question of therapists' differential effectiveness: a Sheffield Psychotherapy Project addendum 383–385

Shavit, N. *see* **Leff, J.** *et al* 58–66

Shaw, Mike *see* **Appleby, Louis** *et al* 510–515

Shering, P. Anne *see* **Scott, Allan I. F.** 853–857

Shiwach, R. S. and **Crocker, M.** Sex chromosomes and psychosis (C) 722–723

Shrimankar, J. *et al.* Dexamethasone suppression test in dementia and depression: clinical and biological correlates 372–377

Shukla, G. D. 'Asneezia' – some further observations 689–690

Signer, S. F. Delusions of inanimate doubles (C) 573

Signer, Stephen F. Homo-erotomania (C) 729

Sillince, C. *see* **Abbott, P. M.** *et al* (C) 730

Silverstone, Trevor and **Romans-Clarkson, Sarah.** Bipolar affective disorder, causes and prevention of relapse (*Review article*) 321–335

Simpson, C. J. *et al.* The chronically mentally ill in community facilities: a study of quality of life 77–82

Simpson, K. H. and **Snaith, R. P.** The use of propofol for anaesthesia during ECT (C) 721–722

Smeetin, Nigel and **Wilkinson, Greg.** Repetition of parasuicide (C) 720

Smith, Jane E. *see* **Daniel, Walter F.** *et al* (C) 274–275

Smyth, Marcellino and **Craddock, Nick.** Hospital suicides (C) 728

Snaith, R. P. *see* **Simpson, K. H.** (C) 721–722

Snyder, Karen S. *see* **Mintz, Lois Imber** *et al* 212–217

Soni, Som D. *see* **Shrimankar, J.** *et al* 372–377

Spears, Nicki M. *see* **Goldwasser, Harry D.** *et al* (BR) 102–104

Spurrell, Mark *see* **Thomas, Christopher S.** *et al* 83–85

Starkstein, Sergio E. and **Robinson, Robert G.** Affective disorders and cerebral vascular disease (*Review article*) 170–182

Staufenberg, E. F. and **Tantam, D.** Malignant hyperpyrexia syndrome in combined treatment (C) 577–578

Stein, George *see* **Dewsnap, Paul-Allan** (C) 120

Stewart, A. *see* **Newton, J. R.** *et al* (*Case conference*) 691–696

Stiles, William B. *see* **Shapiro, David A.** *et al* 383–385

Stokes, Sudhir. Near-death experience (C) 567

Stone, Jillian *see* **Judd, Fiona K.** *et al* 668–671

Strachan, A. *see* **Leff, J.** *et al* 58–66

Strang, John *see* **Gossop, Michael** *et al* 360–363

Sundarum, K. R. *see* **Deshpande, S. N.** *et al* 504–509

Szasz, Thomas. 1. Psychiatric justice (*Point of view*) 864–869

Szmukler, George I. The Melbourne Maudsleys (C) 887–888

Tandon, Rajiv *et al.* Cholinergic syndrome following anticholinergic withdrawal in a schizophrenic patient abusing marijuana (BR) 712–714

Tantam, D. *see* **Staufenberg, E. F.** (C) 577–578

Tarrier, N. *see* **Bishay, N. R.** *et al* 386–389

Tarrier, Nicholas *et al.* Community management of schizophrenia: a two-year follow-up of a behavioural intervention with families 625–628

Taylor, Graeme *et al.* Psychological-mindedness and the alexithymia construct (C) 731–732

Taylor, F. Kräupl. The damnation of benzodiazepines (*Point of view*) 697–704

Tennant, Chris *see* **Bernardi, Elsa** *et al* 677–682

Thivierge, Jacques *see* **Maziade, Michel** *et al* 535–543, 544–551

Thomas, Christopher S. *et al.* Severity of withdrawal in subjects exposed to a combination of alcohol and minor tranquillisers 83–85

Thomas, R. Chronic depression (C) 124–125

Thomas, Roger *see* **Harris, Brian** *et al* 660–667, 813–817

Timney, Brian R. Positive symptoms of schizophrenia (C) 268

Todd, John. AIDS as a current psychopathological theme: a report on five heterosexual patients (BR) 253–255

Tomison, Arden R. Characteristics of psychiatric hospital absconders 368–371

Trachtenberg, Dvora D. *see* **Ennis, Jon** *et al* 41–47

Trivedi, J. R. *see* **Verghese, A.** *et al* 499–503

Turkington, Douglas *see* **Drummond, D. Colin** (C) 571–572

Turner, Stuart *et al.* Wernicke's encephalopathy in an 18-year-old woman (BR) 261–262

Tweed, J. Lindsey *et al.* The effects of childhood parental death and divorce on six-month history of anxiety disorders 823–828

Tyrer, Peter *see* **Murphy, Siobhan M.** *et al* 529–534

Vásquez-Barquero, J. L. *see* **Briscoe, M. E.** *et al* 364–367

Vaughn, C. *see* **Leff, J.** *et al* 58–66

Vaughn, Christine *see* **Tarrier, Nicholas** *et al* 625–628

Verduyn, C. *see* **Allsopp, M.** 829–834

Verghese, A. *et al.* Factors associated with the course and outcome of schizophrenia in India: results of a two-year multicentre follow-up study 499–503

Volans, N. *see* **Hutchesson, E. A.** 34–40

Waddington, John. Sight and insight: brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography (*Annotation*) 433–436

Wafer, K. *see* **McDonald, J.** (C) 420–421

Walker, Richard *see* **Harris, Brian** *et al* 660–667

Warburton, David *see* **Sahakian, Barbara** *et al* 797–800

Warneke, Lorne B. Pre-pubertal depressive stupor (C) 418–419

Watts, Susan *see* **Tarrier, Nicholas** *et al* 625–628

Webb, Marcus *see* **Yatham, Lakshmi N.** *et al* (C) 879

Webber, John E. *see* **Judd, Fiona K.** *et al* 668–671

Weeks, David J. 'Normal' eccentrics (C) 410–411

West, D. J. 2. Szasz on psychiatric justice (*Point of view*) 870–871

White, A. C. Post-traumatic stress (C) 886–887

Whittington, R. M. *see* **Goh, Seng Eng** *et al* 247–249

Widiger, T. Psychiatrists' responses to personality disorder (C) 266

Wig, N. N. *see* **Deshpande, S. N.** *et al* 504–509

Wildgrube, C. *see* **Priebe, S.** *et al* 396–399

Wilkinson, Greg. Referrals from general practitioners to psychiatrists and paramedical mental health professionals 72–76

Wilkinson, Greg and **Markus, A. C.** PROQSY: a computerised technique for psychiatric case identification in general practice 378–382

Wilkinson, Greg *see* **Smeeton, Nigel** (C) 720

Williams, P. *see* **Briscoe, M. E.** *et al* 364–367

Williams, Paul and **Balestrieri, Matteo.** Psychiatric clinics in general practice: do they reduce admissions? 67–71

Wilmotte, J. *see* **Schittecatte, M.** *et al* 858–863

Wilson, Janet A. *see* **Deary, I. J.** (C) 727–728

Wittchen, H. U. *see* **Moller, H. J.** *et al* 467–472

Wolf, B. *see* **Schmidt, L. G.** *et al* 839–843

Wright, Simon and **Peet, Malcolm.** Gilles de la Tourette's syndrome: amelioration following acute akinesia during lorazepam withdrawal (BR) 257–259

Wylie, K. R. *et al.* Lofrepramine-induced hyponataemia (C) 419–420

Yatham, Lakshmi N. *et al.* Which patients will respond to ECT? (C) 879

Yeo, Ronald A. *see* **Daniel, Walter F.** *et al* (C) 274–275

Young, Allan and **Kehoe, Robert.** Two cases of agranulocytosis on addition of a butyrophenone to a long-standing course of phenothiazine treatment (BR) 710–712

Zaudig, M. *see* **Moller, H. J.** *et al* 467–472

Zerssen, D. von *see* **Moller, H. J.** *et al* 467–472

Zuuren, Florence J. van The fear questionnaire (C) 726–727.

PART III. BOOK REVIEWS

AIDS

Bridge, Peter, Mirsky, Allen F. and **Goodwin, Frederick K.** (eds). Psychological, neuropsychotic and substance abuse aspects of AIDS. (David Goldmeier) 142

ALCOHOLISM

Annis, Helen M., Graham, J. Martin and **Davis, Christine S.** Inventory of drinking situations: users' guide. (Jonathan Chick) 279–280

Skinner, Harvey A. and **Holt, Stephen.** The alcohol clinical index: strategies for identifying patients with alcohol problems. (Jonathan Chick) 279

Steinglass, Peter with **Bennett, Linda A., Wolin, Steven J.** and **Reiss, David.** The alcoholic family: drinking problems in a family context. (Douglas Cameron) 586

BIOLOGICAL PSYCHIATRY

Abrams, Richard. Electroconvulsive therapy. (R. P. Snaith) 898

Kiloh, L. G., Smith, J. S. and **Johnson, G. F.** Physical treatment in psychiatry. (John Pollitt) 143

Trimble, Michael R. Biological psychiatry. (Kenneth Davison) 278–279

CHILD AND ADOLESCENT PSYCHIATRY

Looney, John G. (ed.). Chronic mental illness in children and adolescents. (T. P. Berney) 138–139

Popper, Charles (ed.). Psychiatric pharmacosciences of children and adolescents. (I. M. Goodyer) 426

Sarnoff, Charles A. Psychotherapeutic strategies in late latency through early adolescence. (Mark Aveline) 135

Sarnoff, Charles A. Psychotherapeutic strategies in the latency years. (Mark Aveline) 135

CHILD PSYCHIATRY

Adams, Paul L. and **Fras, Ivan** (eds). Beginning child psychiatry. (David Cottrell) 281–282

Bean-Bayog, Margaret and **Stimmel, Barry** (eds). Children of alcoholics. (Peter Anderson) 129

Browne, Kevin, Davies, Cliff and **Stratton, Peter** (eds). Early prediction and prevention of child abuse. (Ian Berg) 588

Chess, Stella, Thomas, Alexander and **Hertzig, Margaret** (eds). Annual progress in child psychiatry and child development – 1987. (Philip Barker) 583

Hoghughi, Masud *et al.* Treating problem children: issues, methods and practice. (Pamela Wills) 584–585

Minty, Brian and **Ashcroft, Colin.** Child care and adult crime. (E. Carol Sheldrick) 427

Schetky, Diane H. and **Green, Arthur H.** Child sexual abuse: a handbook for health care and legal professionals. (Stephen Wolkind) 427–428

Schetky, Diane H. and **Green, Arthur H.** (eds). Child sexual abuse: a handbook for health care and legal professionals. (D. J. West) 581

Winnicott, D. W. Babies and their mothers (Phil Mollon) 902

COMMUNITY PSYCHIATRY

Bloor, Michael, McKeganey, Neil and **Fonkert, Dick.** One food in Eden: a sociological study of the range of therapeutic community practice. (Tom Burns) 895–896

Dorfman, Rachelle (ed.). Paradigms of clinical social work. (Herschel Prins) 897–898

Lavender, Anthony and **Holloway, Frank** (eds). Community care in practice – services for the continuing care client. (Lawrence, R. E.) 899–900

COMPUTER MODELS

Boden, Margaret. Computer models of the mind: computational approaches in theoretical psychology. (Robert West) 746–747

Chard, Tim. Computing for clinicians. (Colin Cooper) 897

CROSS-CULTURAL COMPARISONS

Comas-Diaz, Lillian and **Griffith, Ezra E. H.** (eds). Clinical guidelines in cross cultural mental health. (Bernard Ineichen) 130

Fernando, S. Race and culture in psychiatry. (Linda Gask) 136–137

DEMENTIA

Henderson, A. S. and **Henderson, J. H.** (eds). Etiology of dementia of Alzheimer's type. (Robin Jacoby) 899

DEPRESSION

Kinsbourne, Marcel (ed.). Cerebral hemisphere function in depression. (Anthony David) 896

Kleinman, Arthur. Social origins of distress and disease. (Hugh Freeman) 135–136

Marsella, Anthony J., Hirschfeld, Robert H. A. and **Katz, Martin M.** The measurement of depression. (S. P. Tyrer) 134

EATING DISORDERS

Bhanji, S. and **Mattingly, D.** Medical aspects of anorexia nervosa. (Neil L. Holden) 144–145

Garner, David M. and **Garfinkel, Paul E.** (eds). Diagnostic issues in anorexia nervosa and bulimia nervosa. (Ken Gordon) 144

Hudson, James L. and **Pope, H. G.** (eds). The psychobiology of bulimia. (Neil L. Holden) 144

Pirke, K. M., Vandereycken, W. and **Ploog, D.** (eds). The psychobiology of bulimia nervosa. (Eric Button) 582–583

Scott, Derek (ed.). Anorexia and bulimia nervosa: practical approaches. (Kenneth Gordon) 583–584

EPIDEMIOLOGICAL PSYCHIATRY

Williams, P., Wilkinson, G. and **Rawnsley, K.** (eds). The scope of epidemiological psychiatry. (Mark McCarthy) 895

EPILEPSY

Bruton, C. J. The neuropathology of temporal lobe epilepsy. (D. F. Scott) 131

Pedley, Timothy A. and **Meldrum, Brian S.** (eds). Recent advances in epilepsy (2). (D. F. Scott) 129–130

FAMILY PSYCHIATRY

Bruggen, Peter and **O'Brien, Charles.** Helping families: systems, residential and agency responsibility. (Sally Bonner) 279

Burbatti, Guido L. and **Formenti, Laura.** The Milan approach to family therapy. (Dorothy Heard) 740–741

Gold, Judith H. (ed.). Divorce as a development process. (Nicola Blandford) 749

Hinde, Robert and **Stevenson-Hinde, Joan** (eds). Relationships within families: mutual influences. (Alan Cooklin) 741

Humphrey, Michael and **Humphrey, Heather.** Families with a difference, varieties of surrogate parenthood. (Nigel Beail) 748

MacPhail, Duncan. Family therapy in the community. (Rachel Leheup) 739–740

Michaels, Gerald Y. and **Goldberg, Wendy A.** (eds). The transition to parenthood: current theory and research. (Terry Birchmore) 897

Peters, Ray de V. and **McMahon, Robert J.** (eds). Social learning and systems approaches to marriage and the family. (Sebastian Kraemer) 283

Quinton, David and **Rutter, Michael.** Parenting breakdown – the making and breaking of intergenerational links. (Don McDwyer) 283–284

Visher, Emily and **Kilner, John.** Old loyalties, new ties: therapeutic strategies with stepfamilies. (Gill Gorell Barnes) 282

FORENSIC PSYCHIATRY

Dell, Susanne and **Robertson, Graham.** Sentenced to hospital: offenders in Broadmoor. (Patrick G. McGrath) 426–427

Halleck, Seymour L The mentally disordered offender. (Paul Bowden) 138

Hirsch, Steven R. and **Harris, John** (eds). Consent and the incompetent patient, ethics, law and medicine. (Derek Chiswick) 430–431

Koenraadt, Frans and **Zeegers, Michael** (eds). Trends in law and mental health. (Paul Bowden) 585–586

GENERAL PSYCHIATRY

Burns, Alistair S., David, Anthony S. and **Farrell, Michael.** MCQs and short notes in psychiatry. (J. J. Hart) 282

Cohen, R. I. and **Hare, J. J.** Student psychiatry today: a comprehensive textbook. (Linda Gask) 900–901

Freeman, Chris. MCQs for psychiatric studies. (J. J. Hart) 282–283

Freeman, D. X., Lourie, R. S., Metzler, H. Y., Talbot, J. A. and **Weiner, H.** (eds). The year book of psychiatry and applied mental health. (M. W. P. Carney) 280

Hales, Robert E. and **Frances, Allen J.** (eds). Psychiatry update: American Psychiatric Association annual review. Volume 6. (J. L. Gibbons) 586–587

Hall, Peter and **Stonier, Peter D.** (eds). Perspectives in psychiatry. (Suman J. M. Fernando) 746

Howells, John G. (ed.). Modern perspectives in psychiatry. No. 10. Modern perspectives in clinical psychiatry. (Eva C. Johnstone) 745

McKeon, Patrick and **Gilvarry, Eilish.** Pocket examiner in psychiatry. (Eric Shur) 428–429

Nicholi, Armand M. *Jr* (ed.). The new Harvard guide to psychiatry. (Kenneth Davison) 281

Sensky, Tom (ed.). Learning psychiatry through MCQ: a comprehensive list. (Elaine Arnold) 740

Shea, Shawn C. Psychiatric interviewing: the art of understanding. (G. J. van der Ploeg) 749

Shea, Shawn Christopher. Psychiatric interviewing: the art of understanding. (Jean C. R. Galloway) 430

HISTORY

Castel, Robert. The regulation of madness, the origins of incarceration in France. (Henry Rollin) 744

Hippius, H., Peters, G. and **Plogg, D.** (eds). Emil Kraepelin's memoirs. (T. J. Crow) 127–128

HYPNOSIS

Heap, Michael (ed.). Hypnosis: current clinical, experimental and forensic practice. (H. Mersky) 738

Spiegel, Herbert and **Spiegel, David.** Trance and treatment: clinical uses of hypnosis. (Peter A. McCue) 137

LIAISON PSYCHIATRY

Christodoulou, George N. (ed.). Psychosomatic medicine past and future. (Judith Anderson) 589

Kutscher, Austin H. (ed.). Suffering: psychological and social aspects in loss, grief and care. (K. Bluglass) 739

MENTAL DISORDERS

Bachrach, Leona L. and **Nadelson, Carol C.** Treating chronically mentally ill women. (J. K. W. Morrice) 143–144

Halaris, Angelos (ed.). Chronobiology and psychiatric disorders. (G. J. van der Ploeg) 145

Kidel, Mark and **Rowe-Leete, Susan** (eds). The meaning of illness. (Graham Hart) 284

Kroll, Jerome. The challenge of the borderline patient: competency in diagnosis and treatment. (Alex Tarnopolsky) 134–135

Kurstak, Edouard, Lipowski, Z. J. and **Morozov, P. V.** (eds). Viruses, immunity and mental disorders. (Tom Dening) 139

Miller, Edgar and **Cooper, Peter J.** (eds). Adult abnormal psychology. (Chris Frith) 584

MENTAL HEALTH SERVICES

Golomb, Sylvia L. and **Kocsis, Andrea** (eds). The halfway house: on the road to independence. (D. W. Millard) 141–142

Lystad, Mary. Mental health response to mass emergencies: theory and practice. (Colin M. Parkes) 903

Milne, Derek (ed.). Evaluating mental health practice: methods and applications. (D. P. Forster) 431

Newton, Jennifer. Preventing mental illness. (A. C. Brown) 429–430

Smith, Christopher J. and **Giggs, A.** (eds). Location and stigma: contemporary perspectives on mental health and mental health care (Traolach S. Brugha) 145

NARCOLEPSY

Honda, Y. and **Juji, T.** (eds). HLA in narcolepsy. (D. F. Scott) 901

NEUROSCIENCES

Adams, J. Hume and **Graham, D.** An introduction to neuropathology. (C. J. Bruton) 141

Critchley, E. M. R. Language and speech disorders: a neurophysiological approach. (M. R. Trimble) 428

Franzen, Michael D. and **Lovell, Mark R.** Study guide and self assessment for the American Psychiatric Press

Textbook of Neuropsychiatry. (E. M. R. Critchley) 137–138

Glees, Paul. The human brain. (Anthony Hopkins) 283

Kapur, Narinder. Memory disorders in clinical practice. (Tom Dening) 743–744

Rothstein, Arden, Benjamin, Lawrence, Crosbie, Melvin and **Eisenstedt, Katie.** Learning disorders: an integration of neuropsychological and psychoanalytic considerations. (B. A. Farrell) 900

Tarter, R. E., Thiel, D. H. van and **Edwards, K. L.** (eds). Medical neuropsychology: the impact of disease on behaviour. (C. Katona) 431

NEW EDITIONS

Kendall, R. E. and **Zeally, A. K.** (eds). Companion to psychiatric studies (4th edn). (R. J. Daly) 285

Silverstone, Trevor and **Turner, Paul.** Drug treatment in psychiatry (4th edn). (C. J. Thomas) 285

OLD AGE

Giaquinto, Salvatore. Aging and the nervous system. (Robin Jacoby) 280–281

Levi, Lennart (ed.). Society, stress and disease, Vol. 5: old age. (Brice Pitt) 133–134

Roth, M., Huppert, F. A., Tym, E. and **Mountjoy, C. Q.** CAMDEX: the Cambridge examination for mental disorders of the elderly. (Elaine Murphy) 894–895

PRE-MENSTRUAL SYNDROMES

Gise, Leslie Hartley (ed.). Contemporary issues in obstetrics and gynecology, Volume 2: the premenstrual syndromes. (Hilary Allen) 132

PSYCHOANALYSIS

Bott, Elizabeth (ed.). Melanie Klein today: developments in theory and practice. Volume I: Mainly theory. (Jeremy Holmes) 582

Goldberg, Arnold. A fresh look at psychoanalysis: the view from self psychology. (Anthony Ryle) 747

Haynal, Andre. The technique at issue, controversies in psychoanalysis from Freud and Ferenczi to Michael Balint. (Nina E. C. Coltart) 585

Welldon, Estela V. Mother, madonna, whore, the idealisation and denigration of motherhood. (Zaida Hall) 902–903

PSYCHOLOGY

Colman, Andrew M. Facts, fallacies and frauds in psychology. (Joan Freeman) 142–143

Eisenberg, Nadine and **Glasgow, David** (eds). Current issues in clinical psychology 1986. (Nicholas Tarrier) 588

Glover, Jonathan. I: The philosophy and psychology of personal identity. (Digby Tantum) 130–131

Jain, Uday. The psychological consequences of crowding. (Hugh Freeman) 136

Mathews, Andrew and **Steptoe, Andrew.** Essential psychology for medical practice. (Sean Lynch) 587

Neisser, Ulric and **Winograd, Eugene** (eds). Remembering reconsidered: ecological and traditional approaches to the study of memory. (Ian M. L. Hunter) 581–582

Slade, Peter D. and **Bentall, Richard P.** Sensory deception: a scientific analysis of hallucination. (J. J. Hart) 588–589

Watts, Fraser N. (ed.). New developments in clinical psychology. Vol. 2. (Paul Gilbert) 901–902

Weeks, David J. and **Ward, Kate.** Eccentrics: the scientific investigation. (Gaius Davies) 132–133

Williams, Mark G., Watts, Frazer, N., McLeod, Colin and **Mathews, Andrew.** Cognitive psychology and emotional disorders. (Peter Butcher) 278

PSYCHOPHARMACOLOGY

Birch, N. J. (ed.). Lithium: inorganic pharmacology and psychiatric use. (Elizabeth F. Marshall) 748

Casey, Daniel E. and **Christensen, A. Vibeke** (eds). Psychopharmacology: current trends. (Malcolm Peet) 739

Donovan, Bernard T. Humors, hormones and the mind. (R. J. Dolan) 139–140

Iverson, L. L., Iverson, S. D. and **Snyder, S. H.** (eds). Handbook of psychopharmacology. Vol. 20. Psychopharmacology of the aging nervous system. (John M. Kellett) 745–746

McElroy, Susan L. and **Pope, Harrison G.** (eds). Use of anticonvulsants in psychiatry: recent advances. (Malcolm Peet) 133

Rodgers, R. J. and **Cooper, S. J.** (eds). Endorphins, opiates and behavioural processes. (Andrew Johns) 128–129

PSYCHOTHERAPY

Carnwath, T. and **Millar, D.** Behavioural psychotherapy in primary care: a practice manual. (Greg Wilkinson) 741–742

Ebaugh, Helen. Becoming an ex: the process of role exit. (Sidney Crown) 903

Flores, Philip J. Group psychotherapy with addicted populations. (Andrew Johns) 128

Goodrich, Thelma Jane, Rampage, Cheryl, Ellman, Barbara and **Halstead, Kris.** Feminist family therapy: a casebook. (Margaret J. Little) 129

Kaplan, Bert L. The art of intervention in dynamic psychotherapy. (N. D. Macaskill) 747–748

Lichstein, Kenneth L. Clinical relaxation strategies. (Julian Fuller) 744–745

Mann, James and **Goldman, Robert.** A casebook in time-limited psychotherapy. (David Fainman) 589

Peseschkian, Nossrat. Positive psychotherapy: therapy and practice of a new method. (Rachel Leheup) 133

Sidoli, Mara and **Davies, Miranda** (eds). Jungian child psychotherapy. (Elizabeth Gee) 898–899

Trower, Peter, Casey, Andrew and **Dryden, Windy.** Cognitive-behavioural counselling in action. (Duncan Cramer) 137

RELIGION AND ETHICS

Davies, Gaius. Stress – the challenge to Christian caring. (Louis Marteau) 282

Dyer, Allen R. Ethics and psychiatry: toward professional definition. (R. A. Hope) 284–285
Lakin, Martin. Ethical issues in the psychotherapies. (Jane Campbell) 587–588
Robinson, Lillian H. (ed.). Psychiatry and religion: overlapping concerns. (Bernadette Murphy) 429
RESEARCH
Gordon, Richard E., Hursch, Carol J. and **Gordon, Katherine K.** An introduction to psychiatric research. (David Goldberg) 743
Greist, John H., Carroll, Judith A., Erdman, Harold P., Klein, Marjorie H. and **Wurster, Cecil R.** (eds). Research in mental health computing: the next five years. (Mark MacCarthy) 430

SCHIZOPHRENIA
Bebbington, Paul and **McGuffin, Peter** (eds). Schizophrenia: the major issues. (Thomas Bewley) 742–743
Birchwood, Max, Hallett, Stephen and **Preston, Martin.** Schizophrenia: an integrated approach to research and treatment. (Hugh Freeman) 131–132
Hafner, H., Gattarz, W. F. and **Janzarik, W.** Search for the causes of schizophrenia. (Hugh Freeman) 140–141

Supplement 4, Volume 154

PART I. SUBJECTS

Adrenoceptors. The platelet α_2-adrenoceptor as a potential biological marker in depression. Jesús A. García-Sevilla 67–72

America.
- Comparative distributions of DSM–III diagnoses in North and South American clinical samples. Cecilia Sogi *et al* 91–95
- International diagnostic systems and Latin-American contributions and issues. Juan E. Mezzich 84–90

Anxiety disorders. The classification of anxiety disorders. M. G. Gelder 28–32

Cambridgeshire. Obsessive–compulsive disorders in Cambridgeshire: a follow-up study of up to 20 years. G. E. Berrios and H. Chiu 17–20

Cerebral hemispheres. Vocal acoustic correlates of flat affect in schizophrenia: similarity to Parkinson's disease and right hemisphere disease and contrast with depression. M. Alpert *et al* 51–56

Classifications.
- An overview of the prospective ICD–10 classification of mental disorders. J. E. Cooper 21–23
- The classification of anxiety disorders. M. G. Gelder 28–32

Concepts.
- A new concept of the relationship between psychological coping mechanisms and biological stress buffering systems. Arnold J. Friedhoff and Philip Simkowitz 61–66
- The concept of perversion in psychoanalysis. R. H. Etchegoyen 81–83
- The development of the concept of reactive psychoses. Eric Strömgren 47–50

Coping. A new concept of the relationship between psychological coping mechanisms and biological stress buffering systems. Arnold J. Friedhoff and Philip Simkowitz 61–66

Dementia. Non-cognitive symptoms and the diagnosis of dementia: historical and clinical aspects. G. E. Berrios 11–16

Depression.
- Neuroendocrine challenges in the diagnosis of depressive disorders. J. J. López-Ibor *et al* 73–76
- The platelet α_2-adrenoceptor as a potential biological marker in depression. Jesús A. García-Sevilla 67–72
- Vocal acoustic correlates of flat affect in schizophrenia: similarity to Parkinson's disease and right hemisphere disease and contrast with depression. M. Alpert *et al* 51–56

Diagnoses.
- Comparative distributions of DSM–III diagnoses in North and South American clinical samples. Cecilia Sogi *et al* 91–95
- International diagnostic systems and Latin-American contributions and issues. Juan E. Mezzich 84–90
- Neuroendocrine challenges in the diagnosis of depressive disorders. J. J. López-Ibor *et al* 73–76
- Non-cognitive symptoms and the diagnosis of dementia: historical and clinical aspects. G. E. Berrios 11–16
- On multiaxial psychiatric diagnosis for general medical patients. A. Lobo 38–41
- The biases of psychiatric diagnosis. José Guimón 33–37
- The diagnosis of public mental health care bureaucracies. Luis Rojas Marcos and Rosa M. Gil 96–100

Dopamine.
- A new concept of the relationship between psychological coping mechanisms and biological stress buffering systems. Arnold J. Friedhoff and Philip Simkowitz 61–66
- Dopaminergic balance and subtypes of schizophrenia. R. Dávila *et al* 57–60

DSM–III. Comparative distributions of DSM–III diagnoses in North and South American clinical samples. Cecilia Sogi *et al* 91–95

Epidemiology. Unexplained physical complaints: psychopathology and epidemiological correlates. Javier I. Escobar and Gloriosa Canino 24–27

Follow-up. Obsessive–compulsive disorders in Cambridgeshire: a follow-up study of up to 20 years. G. E. Berrios and H. Chiu 17–22

Hydrocephalus. Psychiatric aspects of normal-pressure hydrocephalus: a report of five cases. J. Pujol *et al* 77–80

ICD–10. An overview of the prospective ICD–10 classification of mental disorders. J. E. Cooper 21–23

Markers. The platelet α_2-adrenoceptor as a potential biological marker in depression. Jesús A. García-Sevilla 67–72

Medicine: general. On multiaxial psychiatric diagnosis for general medical patients. A. Lobo 38–41

Mental disorders *see* **Psychiatric disorders.**
Mental health care. The diagnosis of public mental health care bureaucracies. Luis Rojas Marcos and Rosa M. Gil 96–100

Neuroendocrinology. Neuroendocrine challenges in the diagnosis of depressive disorders. J. J. López-Ibor *et al* 73–76

Obsessive–compulsive disorders. Obsessive–compulsive disorders in Cambridgeshire: a follow-up study of up to 20 years. G. E. Berrios and H. Chiu 17–20

Parkinson's disease. Vocal acoustic correlates of flat affect in schizophrenia: similarity to Parkinson's disease and right hemisphere disease and contrast with depression. M. Alpert *et al* 51–56
Perversions. The concept of perversion in psychoanalysis. R. H. Etchegoyen 81–83
Physical complaints. Unexplained physical complaints: psychopathology and epidemiological correlates. Javier I. Escobar and Gloriosa Canino 24–27
Platelets. The platelet α_2-adrenoceptor as a potential biological marker in depression. Jesús A. García-Sevilla 67–72
Psychiatric disorders.
  An empirical prototypical approach to the definition of psychiatric illness. Juan E. Mezzich 42–46
  An overview of the prospective ICD–10 classification of mental disorders. J. E. Cooper 21–23
Psychoanalysis. The concept of perversion in psychoanalysis. R. H. Etchegoyen 81–83
Psychopathology. Unexplained physical complaints: psychopathology and epidemiological correlates. Javier I. Escobar and Gloriosa Canino 24–27
Psychoses. The development of the concept of reactive psychoses. Eric Strömgren 47–50

Schizophrenia.
  Dopaminergic balance and subtypes of schizophrenia. R. Davila *et al* 57–60
  Vocal acoustic correlates of flat affect in schizophrenia: similarity to Parkinson's disease and right hemisphere disease and contrast with depression. M. Alpert *et al* 51–56
Stress. A new concept of the relationship between psychological coping mechanisms and biological stress buffering systems. Arnold J. Friedhoff and Philip Simkowitz 61–66
Symptoms.
  Non-cognitive symptoms and the diagnosis of dementia: historical and clinical aspects. G. E. Berrios 11–16
  Unexplained physical complaints: psychopathology and epidemiological correlates. Javier I. Escobar and Gloriosa Canino 24–27

PART II. CONTRIBUTORS

Ahn, Chul W. *see* **Sogi, Cecilia** *et al* 91–95
Alpert, M. *et al.* Vocal acoustic correlates of flat affect in schizophrenia: similarity to Parkinson's disease and right hemisphere disease and contrast with depression 51–56
Andia I. *see* **Davila, R.** *et al* 57–60

Barcena, B. *see* **Davila, R.** *et al* 57–60
Berrios, G. E. and **Chiu, H.** Obsessive–compulsive disorders in Cambridgeshire: a follow-up study of up to 20 years 17–20
Berrios, G. E. Non-cognitive symptoms and the diagnosis of dementia: historical and clinical aspects 11–16
Borod, J. C. *see* **Alpert, M.** *et al* 51–56

Canino, Gloriosa *see* **Escobar, Javier, I.** 24–27
Chiu, H. *see* **Berrios, G. E.** 17–20
Conde, C. *see* **Pujol, J.** *et al* 77–80
Cooper, J. E. An overview of the prospective ICD–10 classification of mental disorders 21–23

Davila, R. *et al.* Dopaminergic balance and subtypes of schizophrenia 57–60

Escobar, Javier I. and **Canino, Gloriosa.** Unexplained physical complaints: psychopathology and epidemiological correlates 24–27
Etchegoyen, R. H. The concept of perversion in psychoanalysis 81–83

Fluvia, X. *see* **Pujol, J.** *et al* 77–80
Friedhoff, Arnold J. and **Simkowitz, Philip.** A new conception of the relationship between psychological coping mechanisms and biological stress buffering systems 61–66

García-Sevilla, Jesús A. The platelet α_2-adrenoceptor as a potential biological marker in depression 67–72
Gelder, M. G. The classification of anxiety disorders 28–32
Gil, Rosa M. *see* **Marcos, Luis Rojas** 96–100
Guimón, J. *see* **Savila, R.** *et al* 57–60
Guimón, José. The biases of psychiatric diagnosis 33–37

Iglesias, L. Moral *see* **López-Ibor, Jr, J. J.** *et al* 73–76

Leal, S. *see* **Pujol, J.** *et al* 77–80
Lobo, A. On multiaxial psychiatric diagnosis for general medical patients 38–41
López-Ibor, Jr, J. J. *et al* Neuroendocrine challenges in the diagnosis of depressive disorders 73–76

Manero, E. *see* **Davila, R.** *et al* 57–60
Marcos, Luis Rojas and **Gil, Rosa M.** The diagnosis of public mental health care bureaucracies 96–100
Mezzich, Juan E. An empirical prototypical approach to the definition of psychiatric illness 42–46
Mezzich, Juan E. International diagnostic systems and Latin-American contributions and issues 84–90
Mezzich, Juan E. *see* **Sogi, Cecilia** *et al* 91–95

Retuerto, F. *see* **Davila, R.** *et al* 57–60
Rosen, A. *see* **Alpert, M.** *et al* 51–56

Saavedra-Castillo, Alfredo *see* **Sogi, Cecilia** *et al* 91–95
Saiz-Ruiz, J. *see* **López-Ibor, Jr, J. J.** *et al* 73–76
Simkowitz, Philip *see* **Friedhoff, Arnold J.** 61–66
Sobin, C. *see* **Alpert, M.** *et al* 51–56
Sogi, Cecilia *et al.* Comparative distributions of DSM–III diagnoses in North and South American clinical samples 91–95
Strömgren, Erik. The development of the concept of reactive psychoses 47–50

Valverde, Jesús *see* **Sogi, Cecilia** *et al* 91–95

Warthon, Dante *see* **Sogi, Cecilia** *et al* 91–95
Welkowitz, J. *see* **Alpert, M.** *et al* 51–56

Zumarraga, M. *see* **Davila, R.** *et al* 57–60

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INDEX TO VOLUME 158

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Index to Volume 158

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PART I – SUBJECTS 2–16
PART II – CONTRIBUTORS 16–24
PART III – BOOK REVIEWS 24–27
SUPPLEMENT 10, VOLUME 158 28–29
ACKNOWLEDGEMENT TO ASSESSORS 30–31

Abbreviations: BR Brief Report; C Correspondence; other abbreviations given in text of index.

PART I. SUBJECTS

A hundred years ago
  Harveian Society. General paralysis of the insane. Dr Savage. (Henry Rollin) 138
  Hysteria and organic disease. Henry Rollin 438
  Music as a remedy. Henry Rollin 578
  Nursing of the insane. Henry Rollin 722
  Our library table: *Oeuvres Complètes de J. M. Charcot.* Tome IX. Henry Rollin 867
  The non-restraint question. Henry Rollin 292
Accident and emergency ward. Psychiatric screening of admissions to an accident and emergency ward. Gary Bell *et al* 554–557
Adolescence
  Sex differences in suicidal behaviour of referred adolescents. Joseph M. Rey and Kevin D. Bird 776–781
  see also **Child and adolescent psychiatry**
Adoption. Adoption and eating disorders: a high-risk group? Neil L. Holden 829–833
Adversity. Groups with an increased risk of minor affective disorder. P. E. Bebbington *et al* 33–40
Affective disorders
  Complications
    Bipolar affective disorder following head injury. J. S. Bamrah and J. Johnson (BR) 117–119
    Mood disorders in the year after first stroke. Allan House *et al* 83–92
    Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizoaffective disorders. Ming T. Tsuang 165–170
  Incidence. Gender, parity and the prevalence of minor affective disorder. P. E. Bebbington *et al* 40–45
  Psychology
    Adversity in groups with an increased risk of minor affective disorder. P. E. Bebbington *et al* 33–40
    Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis. Alice Foerster *et al* 171–176
  Therapy. Long-term effects of lithium on the kidney. O. Hetmar *et al* 53–58
  see also **Anxiety, Bipolar disorder, Depression, Dysthymia, Hypomania, Mania** and **Manic depression**
Afro-Caribbeans. Management of first episode psychotic illness in Afro-Caribbean patients. Eric Y. H. Chen *et al* 517–522
Alcoholism
  Carbamazepine in alcohol withdrawal. C. G. Ballard *et al* (C) 133
  Depression and previous alcoholism in the elderly. Brian L. Cook *et al* 72–75
  Who was Jellinek? Griffith Edwards (C) 431
Alprazolam. Prescription-event monitoring of 10 895 patients treated with alprazolam. J. Guy Edwards *et al* 387–392
Alzheimer's disease
  Cerebral pharmacodynamics of physostigmine in Alzheimer's disease investigated using single-photon computerised tomography. R. Hunter *et al* 351–357
  Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. Ken Wilson *et al* (*Current literature*) 558–562
  Evidence for allelic heterogeneity in familial early-onset Alzheimer's disease. Cornelia M. van Duijn *et al* 471–474
  Primitive reflexes in Alzheimer's disease. Paul Crichton and Carrick McDonald (C) 436
Amnesia. Mr X – a case of amnesia. Yair Domb and Katja Beaman (BR) 423–425
Annotations
  Confusions concerning sleep disorders and the epilepsies in children and adolescents. Gregory Stores 1–7
  Genetic model compatible with a dimensional view of schizophrenia. David Roberts and Gordon Claridge 451–456
  Marketing of 5-hydroxytryptamine: depression or anxiety? David Healy 737–742

Anorexia nervosa
  - Anorexia in the elderly. Paul Cosford and Elaine Arnold (C) 286–287
  - Anorexia nervosa: outcome and prognostic factors after 20 years. R. H. Ratnasuriya *et al* 495–502
  - Anorexia nervosa across cultures. Sing Lee (C) 284–285, Lawrence McGibbon *et al* (C) 285, Dinesh K. Arya (C) 285–286
  - Anorexia nervosa in the elderly. Brian O'Shea (C) 716–717
  - Anorexia nervosa in a group of Asian children living in Britain. Rachel Bryant-Waugh and Bryan Lask 229–233

Anxiety
  - Bradford Somatic Inventory. Multi-ethnic inventory of somatic symptoms reported by anxious and depressed patients in Britain and the Indo-Pakistan subcontinent. D. B. Mumford *et al* 379–386
  - Controlled comparison of day-patient and out-patient treatment for persistent anxiety and depression. Peter H. Dick *et al* 24–27
  - Longitudinal study of psychological and social factors affecting recovery from psychiatric breakdowns. Keith Oatley and Christina Perring 28–32
  - Marketing of 5-hydroxytryptamine: depression or anxiety? David Healy (*Annotation*) 737–742
  - Social influences on the course of anxious and depressive disorders in school-age children. Ian Goodyer *et al* 676–684

Asians
  - Anorexia nervosa in Asian children. Rachel Bryant-Waugh and Bryan Lask 229–233
  - Eating disorders in Asian women. Sing Lee (C) 131–132
  - Eating disorders in Asians. Santosh K. Chaturvedi (C) 860–861, David B. Mumford (C) 861
  - Sociocultural correlates of eating disorders among Asian schoolgirls in Bradford. D. B. Mumford *et al* 222–228
  - Survey of psychiatrically ill children. Syed Hasan Jawed (BR) 268–270

Audits. In-patient behavioural psychotherapy unit. Description and audit. Graham Thornicroft *et al* 362–367

Australia. British and Australian depression revisited. Alan S. Lee and Conor F. Duggan (C) 287–288

Autism. Is autism more common now than ten years ago? Christopher Gillberg *et al* 403–409

Avon probation service. Berkeley Group. Ten years' experience of a group for non-violent sex offenders. David A. G. Cook *et al* 238–243

Behaviour disorder. Behaviour disorder in pre-school children in Hong Kong. A two-stage epidemiological study. Siu-Luen Luk *et al* 213–221

Behaviour Screening Questionnaire (BSQ). Behaviour disorder in Hong Kong pre-school children. Siu-Luen Luk *et al* 213–221

Behaviour therapy
  - Exposure therapy for post-traumatic stress disorder. Four case studies. David A. Richards and John S. Rose (BR) 836–840
  - In-patient behavioural psychotherapy unit. Description and audit. Graham Thornicroft *et al* 362–367

Belief. Effects of belief on grief. Dave Hambridge (C) 291

Benzodiazepine
  - Benzodiazepine withdrawal syndrome. Malcolm Lader and Sally Morton (C) 435–436
  - Buspirone in benzodiazepine withdrawal. C. H. Ashton *et al* (C) 283–284
  - Double-blind comparison of the effects of gradual withdrawal of lorazapam, diazepam and bromazepam in benzodiazepine dependence. Siobhan M. Murphy and Peter Tyrer 511–516

Berkeley Group. Ten years' experience of a group for non-violent sex offenders. David A. G. Cook *et al* 238–243

Beta-endorphin. Neuropeptide concentrations in CSF before and after ECT. Charles B. Nemeroff *et al* 59–63

Bipolar disorder
  - Bipolar disorder and cerebral sarcoidosis. Declan McLoughlin and Patrick McKeon (BR) 410–413
  - Retrospective case-note study of bipolar disorder in old age. John Snowdon 485–490

Bismuth nitrate. Encephalopathy resembling Creutzfeldt–Jakob disease following oral, prescribed doses of bismuth nitrate. Michael J. von Bose and Michael Zaudig (BR) 278–280

Body Shape Questionnaire. Eating disorders among Asian schoolgirls. D. B. Mumford *et al* 222–228

Books reconsidered
  - *La Schizophrènie*: E. Minkowski. (John Cutting) 293–295
  - *On Becoming a Person: A Therapist's View of Psychotherapy*: Carl Ransom Rogers. (Duncan Cramer) 139–141
  - *One Flesh: Separate Persons*: Robin Skynner. (Stan Ruszczynski) 868–870

Borderline disorders. Borderline and schizotypal disorders in children and adolescents. Martijn Meijer and Philip D. A. Treffers 205–212

Bradford. Eating disorders among Asian schoolgirls. D. B. Mumford *et al* 222–228

Bradford Somatic Inventory. Multi-ethnic inventory of somatic symptoms reported by anxious and depressed patients in Britain and the Indo-Pakistan subcontinent. D. B. Mumford *et al* 379–386

Brain
  - Auditory selective attention and event-related potentials in schizophrenia. Philip B. Ward *et al* 534–539
  - Brain lesions and cognitive function in late-life psychosis. Bruce L. Miller *et al* 76–82. Alistair Flint *et al* (C) 866
  - MRI study of schizophrenia. Brain structure and clinical symptoms. A. H. Young *et al* 158–164
  - Ordering thoughts on thought disorder. John McGrath 307–316
  - Parietal signs and sinister prognosis in dementia. A four-year follow-up study. Ronan O'Carroll *et al* 358–361
  - Schizophrenia: a neuropathological perspective. G. W. Roberts (*Review article*) 8–17
  - *see also* **Cerebrum, Frontal lobes, Parietal lobes** and **Pituitary tumours**

Bristol. Suicide and unexpected deaths among psychiatric in-patients. The Bristol confidential inquiry. H. G. Morgan and Pamela Priest 368–374

Britain

Anorexia nervosa in Asian children. Rachel Bryant-Waugh and Bryan Lask 229–233

British and Australian depression revisited. Alan S. Lee and Conor F. Duggan (C) 287–288

see also **England and Wales**

Bromazepam. Double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. Siobhan M. Murphy and Peter Tyrer 511–516

Bromocriptine. Bromocriptine in catatonic stupor. Tariq Mahmood (C) 437–438

Bromolisuride. Estimated density of D_2 striatal receptors in schizophrenia. A study with positron emission tomography and ^{76}Br-bromolisuride. J. L. Martinot *et al* 346–350

Bulimia nervosa. Bulimia nervosa: family size, sibling sex and birth order. A catchment-area study. J. Hubert Lacey *et al* 491–494

Buspirone

Buspirone in benzodiazepine withdrawal. C. H. Ashton *et al* (C) 283–284

Buspirone in detoxification. Raymond Travers (C) 133–134

Buspirone-induced mania. Ronan J. McIvor and Kenneth Sinanan (C) 136–137

Cancer. Factor structure and factor stability of the Hospital Anxiety and Depression Scale in patients with cancer. Stirling Moorey *et al* 255–259

Capgras syndrome. Capgras syndrome. Bron Lipkin (C) 131

Carbamazepine

Carbamazepine in alcohol withdrawal. C. G. Ballard *et al*(C) 133

Carbamazepine and NMS. Fiona Coulter and F. M. Corrigan (C) 434–435

Cardiovascular disease

Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial. David Wheatley and C. Bass (*Current literature*) 264–267

Mood disorder after stroke. Allan House *et al* 83–92

Care needs. Psychiatric symptoms, diagnoses and care needs of 100 mentally handicapped patients. Brian R. Ballinger *et al* 251–254

Case notes. Recording of information in case notes. D. L. F. Dunleavy and P. L. Cornwall (C) 571

Catatonia

Bromocriptine in catatonic stupor. Tariq Mahmood (C) 437–438

Catatonia: harbinger of the neuroleptic malignant syndrome. Denise A. C. White and Ashley H. Robins (BR) 419–421

Catatonia and NMS. T. K. S. Tan and S. H. Ong (C) 858. Denise A. C. White and Ashley H. Robins (C) 858–859. Tim Dalkin and Jo Kennedy (C) 859

Motor, volitional and behavioural disorders in schizophrenia. 1: Assessment using the modified Rogers Scale. C. E. Lund *et al* 323–327

Motor, volitional disorders in schizophrenia. 2: 'Conflict of paradigms' hypothesis. P. J. McKenna *et al* 328–336

CATEGO4. Comparison of CATEGO-derived ICD–8 and DSM–III. Classifications using the Composite International Diagnostic Interview in severely ill subjects. Anne E. Farmer *et al* 177–182

Cerebrospinal fluid. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Charles B. Nemeroff *et al* 59–63

Cerebrum

Cerebral pharmacodynamics of physostigmine in Alzheimer's disease investigated using single-photon computerised tomography. R. Hunter *et al* 351–357

Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. Ken Wilson *et al* (*Current literature*) 558–562

Polycythaemia rubra vera, cerebral ischaemia and depression. Declan Murray and Richard Hodgson (BR) 842–844

Charcot, J. M. *Oeuvres Complètes de J. M. Charcot.* Tome IX. Our library table. Henry Rollin. (*A hundred years ago*) 867

Checklist, Pre-school Behaviour Checklist (PBCL): Behaviour disorder in Hong Kong pre-school children. Siu-Luen Luk *et al* 213–221

Child and adolescent psychiatry

Anorexia nervosa in Asian children. Rachel Bryant-Waugh and Bryan Lask 229–233

Behaviour disorder in pre-school children in Hong Kong. Siu-Luen Luk *et al* 213–221

Borderline and schizotypal disorders in children and adolescents. Martijn Meijer and Philip D. A. Treffers 205–212

Child physical abuse observed. Comparison of families with and without history of child abuse treated in an in-patient family unit. Kevin Healy *et al* 234–237

Child psychiatry in developing countries. Anula D. Nikapota (*Review article*) 743–751

Child and psychiatry liaison services. L. McGibben and C. Ballard (C) 573

Confusions concerning sleep disorders and the epilepsies in children and adolescents. Gregory Stores (*Annotation*) 1–7

Eating disorders among Asian schoolgirls. D. B. Mumford *et al* 222–228

Impact of a liaison service on patterns of referral. Anne McFadyen *et al* 93–96

Is autism more common now than ten years ago? Christopher Gillberg *et al* 403–409

Patient data in child psychiatry. Patrick J. Byrne (C) 572

Pisa syndrome in an adolescent on neuroleptic medication. Jeremy Turk and Bryan Lask (BR) 422–423

Social influences on the course of anxious and depressive disorders in school-age children. Ian Goodyer *et al* 676–684

Survey of psychiatrically ill Asian children. Syed Hasan Jawed (BR) 268–270

- **Childbirth**. Erotomania in relation to childbirth. Samuel I. Cohen (C) 291
- **Cholinergic stimulation**. Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. Ken Wilson *et al* (*Current literature*) 558–562
- **Chromosome 21**. Evidence for allelic heterogeneity in familial early-onset Alzheimer's disease. Cornelia M. van Duijn *et al* 471–474
- **Chronic fatigue syndrome**. Chronic fatigue syndrome. Eric Serra (C) 717
- **Citalopram**. No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine. Bengt-O. Bengtsson *et al* (BR) 853–855
- **Clozapine**
  - Clozapine-treated NMS. M. F. Burrell *et al* (C) 577
  - ECT following clozapine. Stephen J. Masiar and Celeste A. Johns (C) 135–136
  - Effects of clozapine on tardive dyskinesia. Jeffrey A. Liebermann *et al* 503–510
- **Cognition**. Brain lesions and cognitive function in late-life psychosis. Bruce L. Miller *et al* 76–82, Alistair Flint *et al* (C) 866
- **Community care**
  - Care of chronic neurotic out-patients by community psychiatric nurses. A long-term follow-up study. Tom Burns *et al* 685–690
  - Compulsory psychiatric treatment in the community
    - I. Controlled study of compulsory community treatment with extended leave under the Mental Health Act: Special characteristics of patients treated and impact of treatment. Tom Sensky *et al* 792–799
    - II. Controlled study of patients whom psychiatrists would recommend for compulsory treatment in the community. Tom Sensky *et al* 799–804
  - Planning for community care. Long-stay populations of hospitals scheduled for rundown or closure. P. Clifford *et al* 190–196
  - Replacing the mental hospital. Community provision for a district's chronically disabled in domestic environments? David Kingdon *et al* (BR) 113–117
- **Composite International Diagnostic Interview (CIDI)**. Comparison of CATEGO-derived ICD-8 and DSM-III. Classifications using the Composite International Diagnostic Interview in severely ill subjects. Anne E. Farmer *et al* 177–182
- **Compulsory psychiatric treatment in the community**
  - I. Controlled study of compulsory community treatment with extended leave under the Mental Health Act: Special characteristics of patients treated and impact of treatment. Tom Sensky *et al* 792–799
  - II. Controlled study of patients whom psychiatrists would recommend for compulsory treatment in the community. Tom Sensky *et al* 799–804
- **Computerised tomography**. Computerised tomography and schizophrenia. Robert Miller (C) 863
- **Controls**. Selection of controls. Ian Gale (C) 862, Rodney Morice (C) 862–863
- **Coping style**. Changes in patient coping style following individual and family treatment for schizophrenia. Margaret M. Rea *et al* 642–647
- **Coronary heart disease**. Lifestyle heart trial. David Wheatley and C. Bass (*Current literature*) 264–267
- ***Corrigenda***
  - November 1990
    - 777. Linda Beeley *not* Linda Bealey 438
    - 778. Adityanjee – two references 138
  - December 1990
    - 836–837. Legends for Figs 1 & 2 to be reversed
    - 937. Andrew Scull *not* Andrew Skull 438
- **Corticotrophin-releasing factor**. Neuropeptide concentrations in CSF before and after ECT. Charles B. Nemeroff *et al* 59–63
- **Creatinine phosphokinase (CPK)**
  - CPK in NMS. Bridget Craddock *et al* (C) 130
  - Myth of serum creatinine phosphokinase level and neuroleptic malignant syndrome. Adityanjee (*Point of view*) 706–707
- **Creutzfeldt–Jakob disease**
  - Encephalopathy resembling Creutzfeldt–Jakob disease following oral, prescribed doses of bismuth nitrate. Michael J. von Bose and Michael Zaudig (BR) 278–280
  - "Life, Jim, but not as we know it?" Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts (*Review article*) 457–470
- **Crichton Royal**. Demand for psychogeriatric services. D. N. Anderson and H. Phaterpekar (C) 574–575
- **Cross-cultural psychiatry**
  - Anorexia nervosa across cultures. Sing Lee (C) 284–285, Lawrence McGibbon *et al* (C) 285, Dinesh K. Arya (C) 285–286
  - Culture as a confounding variable. Jonathan Evans (C) 133
  - Ethnic minorities and the psychiatric system. Roland Littlewood (C) 433–434
  - The 'new cross-cultural psychiatry'. Roland Littlewood (C) 575–576
  - Transcultural psychiatry. John L. Cox (*Reading about...*) 579–582
  - *see also* **Afro-Caribbeans** and **Asians**
- **Crossover reactions**. No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine. Bengt-O. Bengtsson *et al* (BR) 853–855
- ***Current literature***
  - Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial. David Wheatley and C. Bass 264–267
  - Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. Ken Wilson *et al* 558–562
  - Is schizophrenia disappearing? John M. Eagles 834–835
  - Is sex necessarily a risk factor to depression? Tirril Harris *et al* 708–712

- **Dangerousness**
  - Compulsory psychiatric treatment in the community
    - I. Controlled study of compulsory community treatment with extended leave under the Mental Health Act: Special characteristics of patients treated and impact of treatment. Tom Sensky *et al* 792–799

II. Controlled study of patients whom psychiatrists would recommend for compulsory treatment in the community. Tom Sensky *et al* 799–804

Dangerous mistakes. Nigel Walker (*Maudsley lecture*) 752–757

Databases. Patient data in child psychiatry. Patrick J. Byrne (C) 572

Day care

Controlled comparison of day-patient and out-patient treatment for persistent anxiety and depression. Peter H. Dick *et al* 24–27

Day care in an inner city

I. Characteristics of attenders. Frank Holloway 805–810

II. Quality of the services. Frank Holloway 810–816

Randomised controlled trial of day and in-patient psychiatric treatment. 2: Comparison of two hospitals. Francis Creed *et al* 183–189

Delusions

Erotomania in mental handicap. M. Ghaziuddin and L. Tsai (BR) 127–129

Prevalence of delusional jealousy in different psychiatric disorders. An analysis of 93 cases. M. Soyka *et al* 549–553

Dementia

Dementia with parietal signs. Carrick McDonald (C) 859, Ronan O'Carroll (C) 859–860

"Life, Jim, but not as we know it?" Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts (*Review article*) 457–470

Parietal signs and sinister prognosis in dementia. A four-year follow-up study. Ronan O'Carroll *et al* 358–361

Systemic lupus erythematosus (SLE) and multi-infarct dementia. B. M. Green and K. C. M. Wilson (C) 291–292

Depression

Complications

Depression and previous alcoholism in the elderly. Brian L. Cook *et al* 72–75

Depression-dependent erotomanic delusions in a mentally handicapped woman. M. Ghaziuddin and L. Tsai (BR) 127–129

Encephalopathy resembling Creutzfeldt–Jakob disease following oral, prescribed doses of bismuth nitrate. Michael J. von Bose and Michael Zaudig (BR) 278–280

Polycythaemia rubra vera, cerebral ischaemia and depression. Declan Murray and Richard Hodgson (BR) 842–844

Psychotic depression presenting as status epilepticus. Jean Claude Monfort and Andre Manus (C) 570–571

Incidence

Bradford Somatic Inventory. Multi-ethnic inventory of somatic symptoms reported by anxious and depressed patients in Britain and the Indo-Pakistan subcontinent. D. B. Mumford *et al* 379–386

Depression and the menopause. David Wheatley (C) 431–432, Ernest H. Friedman (C) 432

EPDS by post. Josephine M. Green *et al* (C) 865

Is sex necessarily a risk factor to depression? Tirril Harris *et al* (*Current literature*) 708–712

Menopausal depression. Louis Appleby (C) 864–865

Physiopathology. Neuropeptide concentrations in CSF before and after ECT. Charles B. Nemeroff *et al* 59–63

Prognosis

British and Australian depression revisited. Alan S. Lee and Conor F. Duggan (C) 287–288

Prognosis of depression in old age. P. W. Burvill *et al* 64–71

Psychopathology

Longitudinal study of psychological and social factors affecting recovery from psychiatric breakdowns. Keith Oatley and Christina Perring 28–32

Negative modes of relating, marital quality and depression. John Birtchnell 648–657

Psychotic depression: psychoanalytic psychopathology in relation to treatment and management. Charles Lund 523–528

Relationship between post-natal depression and mother–child interaction. Alan Stein *et al* 46–52

Social influences on the course of anxious and depressive disorders in school-age children. Ian Goodyer *et al* 676–684

Therapy

Controlled comparison of day-patient and out-patient treatment for persistent anxiety and depression. Peter H. Dick *et al* 24–27

Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. F. G. M. Souza and G. M. Goodwin 666–675

Marketing of 5-hydroxytryptamine: depression or anxiety? David Healy (*Annotation*) 737–742

Trazodone-induced transient hypomanic symptoms and their management. S. Jabeen and C. J. Fisher (BR) 275–278

Verapamil in major (psychotic) depression. Raymond M. Jacques and Stephen J. Cox (BR) 124–125

Detention. Dangerous mistakes. Nigel Walker (*Lecture*) 752–757

Detoxification. Buspirone in detoxification. Raymond Travers (C) 133–134

Developing countries. Child psychiatry in developing countries. Anula D. Nikapota (*Review article*) 743–751

Diagnostic Interview schedule (DIS). Is sex necessarily a risk factor to depression? Tirril Harris *et al* (*Current literature*) 708–712

Diazepam

Diazepam abreaction. Adityanjee *et al* (C) 289

Double-blind comparison of the effects of gradual withdrawal of lorazapam, diazepam and bromazepam in benzodiazepine dependence. Siobhan M. Murphy and Peter Tyrer 511–516

Dopamine

Estimated density of D_2 striatal receptors in schizophrenia. A study with positron emission tomography and ^{76}Br-bromolisuride. J. L. Martinot *et al* 346–350

No evidence for a susceptibility locus predisposing to manic depression in the region of the dopamine (D2) receptor gene. Deborah Holmes *et al* 635–641

- **Double-blind trials**. Blinding trials. Duncan Double (C) 573–574
- **Drugs**
  - Addictive
    - Comparison of the withdrawal responses of heroin and methadone addicts during detoxification. Michael Gossop and John Strang 697–699
    - Toluene-related psychosis. Alan Byrne and Terry Zibin (C) 578
  - Anti-Parkinsonian. Drug-induced koro in a non-Chinese man. Eric Chen (C) 721
  - Dependence on monoamine oxidase inhibitors in high dose. Dimitrios Vartzopoulos and Friedrich Krull (BR) 856–857
  - Prescribing in mental handicap hospitals. T. W. Fan (C) 282–283, Stephen Tyrer *et al* 283
  - What happens to patients who frequently harm themselves? A retrospective one-year outcome study. Ruth Stocks and Allan I. F. Scott 375–378
  - *see also* **Alprazolam, Benzodiazepine, Bismuth nitrate, Bromazepam, Bromocriptine, Buspirone, Carbamazepine, Citalopram, Clozapine, Creatinine phosphokinase, Diazepam, Dopamine, Fluoxetine hydrochloride, Fluphenazine, Hydroxytryptamine, Lithium, Lorazepam, L-tryptophan, Neuroleptics, Paroxetine, Physostigmine, Tolbutamide, Tolvon, Trazodone, Verapamil** and **Zimeldine**
- **DSM–III**. Comparison of CATEGO-derived ICD–8 and DSM–III. Classifications using the Composite International Diagnostic Interview in severely ill subjects. Anne E. Farmer *et al* 177–182
- **Dundee**. Psychiatric symptoms, diagnoses and care needs of 100 mentally handicapped patients. Brian R. Ballinger *et al* 251–254
- **Dyskinesia**
  - Facial dyskinesia: a 16-year follow-up study. H. A. McClelland *et al* 691–696
  - *see also* **Tardive dyskinesia**
- **Dysthymia**. Classification and treatment of dysthymia. D. G. M. Murphy (*Point of view*) 106–109
- **Dystonia**. Dystonia – a potential psychiatric pitfall. M. H. Pinto de Azevedo and Margarida Moniz (C) 436

- **Eating Attitudes Test (EAT)**. Eating disorders among Asian schoolgirls. D. B. Mumford *et al* 222–228
- **Eating disorders**
  - Adoption and eating disorders: a high-risk group? Neil L. Holden 829–833
  - Eating disorder in Asian women. Sing Lee (C) 131–132
  - Eating disorders in Asians. Santosh K. Chaturvedi (C) 860–861, David B. Mumford (C) 861
  - Sociocultural correlates of eating disorders among Asian schoolgirls in Bradford. D. B. Mumford *et al* 222–228
  - *see also* **Anorexia nervosa** and **Bulimia nervosa**
- **Edinburgh Postnatal Depression Scale (EPDS)**. EPDS by post. Josephine M. Green *et al* (C) 865
- **Education**
  - Educating the psychiatrist of the 21st century. Harold Bourne (C) 137–138
  - Educational status and neurological abnormalities in schizophrenia. K. S. Shaji (C) 865–866
  - Postgraduate psychiatry. Louis Appleby (*Reading about*) 439–431
- **Elderly**
  - Anorexia in the elderly. Paul Cosford and Elaine Arnold (C) 286–287, Brian O'Shea (C) 716–717
  - Brain lesions and cognitive function in late-life psychosis. Bruce L. Miller *et al* 76–82, Alistair Flint *et al* (C) 866
  - Demand for psychogeriatric services. D. N. Anderson and H. Phaterpekar (C) 574–575
  - Depression and previous alcoholism in the elderly. Brian L. Cook *et al* 72–75
  - How old are the elderly? Prakash Naik (C) 575
  - Prognosis of depression in old age. P. W. Burvill *et al* 64–71
  - Retrospective case-note study of bipolar disorder in old age. John Snowdon 485–490
  - Scottish survey of old long-stay in-patients. R. G. McCreadie *et al* 398–402
- **Electroconvulsive therapy**
  - ECT following clozapine. Stephen J. Masiar and Celeste A. Johns (C) 135–136
  - Failure to convulse with ECT. Garry Walter (C) 716
  - Neuropeptide concentrations in CSF before and after ECT. Charles B. Nemeroff *et al* 59–63
- **Encephalopathy**. Encephalopathy resembling Creutzfeldt–Jakob disease following oral, prescribed doses of bismuth nitrate. Michael J. von Bose and Michael Zaudig (BR) 278–280
- **England and Wales**. Unfit to plead in England and Wales, 1976–88. A survey. D. H. Grubin 540–548
- **Epilepsies**
  - Confusions concerning sleep disorders and the epilepsies in children and adolescents. Gregory Stores (*Annotation*) 1–7
  - Interictal psychopathology in epilepsy. Prevalence and pattern in a Nigerian clinic. Oye Gureje 700–705
  - Psychotic depression presenting as status epilepticus. Jean Claude Monfort and Andre Manus (C) 570–571
- **Erotomania**
  - Depression-dependent erotomanic delusions in a mentally handicapped woman. M. Ghaziuddin and L. Tsai (BR) 127–129
  - Erotomania in relation to childbirth. Samuel I. Cohen (C) 291
- **Event-related potentials**. Auditory ERPS and schizophrenia. Philip B. Ward *et al* 534–539
- **Evoked potentials**. Early cortical tactile-evoked potentials, laterality and schizophrenia. Jane E. Allen *et al* 529–533
- **Exposure therapy**. Exposure therapy for post-traumatic stress disorder. Four case studies. David A. Richards and John S. Rose (BR) 836–840

- **Family history**. Gilles de la Tourette syndrome in the Middle East. Report of a cohort and a multiple affected large pedigree. Mary M. Robertson and M. R. Trimble (BR) 416–419

Family intervention
  Family intervention. Jim Birch (C) 717–718
  Nithsdale schizophrenia surveys. VIII: Do relatives want family intervention – and does it help? R. G. McCreadie *et al* (BR) 110–113

Fetishism. Hypersexuality, fetishism and multiple sclerosis. R.Huws *et al* (BR) 280–281

Fluoxetine hydrochloride. Successful treatment of paraphilic coercive disorder (a rapist) with fluoxetine hydrochloride. Martin P. Kafka (BR) 844–47

Fluphenazine. Plasma levels of fluphenazine in patients receiving fluphenazine decanoate. Relationship to clinical response. Stephen R. Marder *et al* 658–665

Forensic psychiatry
  Dangerous mistakes. Nigel Walker (*Maudsley lecture*) 752–757
  Treatment as an alternative to prosecution: offenders diverted to treatment. David J. Cooke 785–791

Frontal lobes
  Depression and the menopause. Ernest H. Friedman (C) 432
  Ordering thoughts on thought disorder. John McGrath 307–316
  Schizophrenic symptoms and frontal lobe performance. Peter F. Liddle and Danielle L. Morris 340–345
  Selection of controls. Ian Gale (C) 862, Rodney Morice (C) 862–863

Gender
  Gender, parity and the prevalence of minor affective disorder. P. E. Bebbington *et al* 40–45
  Gender-divergent aetiological factors in obsessive–compulsive disorder. Homa F. Noshirvani *et al* 260–263
  Gender-identity clinic patients. N. E. de Taranto *et a* (C) 714–715, Alistair Burns *et al* (C) 715

General Health Questionnaire (GHQ)
  Psychiatric screening of admissions to an accident and emergency ward. Gary Bell *et al* 554–557
  The GHQ and the HAD. T. P.Snaith (C) 433

General paralysis of the insane. Harveian Society. Dr Savage. (Henry Rollin. *A hundred years ago*) 138

Genes
  Evidence for a pseudo-autosomal locus for schizophrenia using the method of affected sibling pairs. J. Collinge *et al* 624–629
  No evidence for a susceptibility locus predisposing to manic depression in the region of the dopamine (D2) receptor gene. Deborah Holmes *et al* 635–641
  No genetic linkage detected for schizophrenia to Xq27–q28. Lynn E. Delisi *et al* 630–634
  Search for the psychosis gene. T. J. Crow (*Molecular biology symposium*) 611–614

Gerstmann-Straussler syndrome. 'Life, Jim, but not as we know it?' Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts (*Review article*) 457–470

Glomerular filtration rate (GFR). Long-term effects of lithium on the kidney. O. Hetmar *et al* 53–58

Goodmayes Network Analysis Questionnaire (GNAQ). Social networks of long-term patients. David Abrahamson (C) 718–719

Grief. Effects of belief on grief. Dave Hambridge (C) 291

Group psychotherapy. Group psychotherapy. Michael Hobbs. (Reading about...) 723–725

Hallucinations. Musical and verbal hallucinations. A. G. Gordon (C) 715–716

Hamilton Rating Scale for Depression. Professor Max Hamilton: an apology. Peter A. van Keep (C) 434

Head injury. Bipolar affective disorder following head injury. J. S. Bamrah and J. Johnson (BR) 117–119

Heroin. Comparison of the withdrawal responses of heroin and methadone addicts during detoxification. Michael Gossop and John Strang 697–699

Heterogeneity. Evidence for allelic heterogeneity in familial early-onset Alzheimer's disease. Cornelia M. van Duijn *et al* 471–474

Hong Kong. Behaviour disorder in pre-school children. Siu-Luen Luk *et al* 213–221

Hospital Anxiety and Depression (HAD) scale
  Factor structure and factor stability of the Hospital Anxiety and Depression Scale in patients with cancer. Stirling Moorey *et al* 255–259
  The GHQ and the HAD. T. P.Snaith (C) 433
  Using the Hospital and Anxiety and Depression Scale to screen for psychiatric disorders in people presenting with deliberate self-harm. D. Hamer *et al* 782–784

Hospitals
  Day v. in-patient treatment. Francis Creed *et al* 183–189
  Planning for community care. Long-stay populations of hospitals scheduled for rundown or closure. P. Clifford *et al* 190–196
  Prescribing in mental handicap hospitals. T. W. Fan (C) 282–283, Stephen Tyrer *et al* 283
  Replacing the mental hospital. Community provision for a district's chronically disabled in domestic environments? David Kingdon *et al* (BR) 113–117

Human leucocyte antigens (HLA)
  Human leucocyte antigens and tardive dyskinesia. K. W. Brown and T. White (BR) 270–272
  Tardive dyskinesia and HLA. Padraigh Wright (C) 863–864

Hydatidiform moles. Psychosis following hydatidiform mole in a patient with recurrent puerperal psychosis. S. W. Hopker and I. F. Brockington (BR) 122–123

Hydroxytryptamine. Marketing of 5–hydroxytryptamine: depression or anxiety. David Healy (*Annotation*) 737–742

Hypersensitive syndrome. No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine. Bengt-O. Bengtsson *et al* (BR) 853–855

Hypersexuality. Hypersexuality, fetishism and multiple sclerosis. R.Huws *et al* (BR) 280–281

Hypomania. Trazodone-induced transient hypomanic symptoms and their management. S. Jabeen and C. J. Fisher (BR) 275–278

Hysteria
  Dystonia – a potential psychiatric pitfall. M. H. Pinto de Azevedo and Margarida Moniz (C) 436
  Hysteria and organic disease. Henry Rollin (*A hundred years ago*) 438

ICD–8. Comparison of CATEGO-derived ICD–8 and DSM–III. Classifications using the Composite International Diagnostic Interview in severely ill subjects. Anne E. Farmer *et al* 177–182
In-patients
  Child physical abuse observed. Comparison of families with and without history of child abuse treated in an in-patient family unit. Kevin Healy *et al* 234–237
  In-patient behavioural psychotherapy unit. Description and audit. Graham Thornicroft *et al* 362–367
  Nature and severity of disabilities in long-stay psychiatric in-patients in South Glamorgan. I. G. Pryce *et al* 817–821
  Randomised controlled trial of day and in-patient psychiatric treatment. 2: Comparison of two hospitals. Francis Creed *et al* 183–189
  Scottish survey of old long-stay in-patients. R. G. McCreadie *et al* 398–402
  Suicide and unexpected deaths among psychiatric in-patients. The Bristol confidential inquiry. H. G. Morgan and Pamela Priest 368–374
Incest. Incestuous abuse in psychiatric patients. Johann Kinzl and Wilfried Biebl (C) 719
India
  Informed consent in India. K. S. Jacob and I. Rajan (C) 576
  Suicide in Indian women. R. K. Chadda *et al* (C) 434
Indo-Pakistan subcontinent. Multi-ethnic inventory of somatic symptoms reported by anxious and depressed patients in Britain and the Indo-Pakistan subcontinent. D. B. Mumford *et al* 379–386
Informed consent. Informed consent in India. K. S. Jacob and I. Rajan (C) 576
Inner cities. Day care in an inner city
  I. Characteristics of attenders. Frank Holloway 805–810
  II. Quality of the services. Frank Holloway 810–816
Intervention programmes. Engagement of relatives in intervention programmes. Julian Leff *et al* (C) 571–572
Inventory. Bradford Somatic Inventory. D. B. Mumford *et al* 379–386

Jacobson's theory of affects and psychotic depression. Psychotic depression: psychoanalytic psychopathology in relation to treatment and management. Charles Lund 523–528
Jarman-8 index. Social deprivation and rates of treated mental disorder. Developing statistical models to predict psychiatric service utilisation. Graham Thornicroft 475–484
Jealousy
  Delusional jealousy in psychiatric disorders. M. Soyka *et al* 549–553
  Jealousy: the pathology of passion. Paul E. Mullen (*Eliot Slater lecture*) 593–601
Jellinek, E. K.. Who was Jellinek? Griffith Edwards (C) 431

Kidneys
  Long-term effects of lithium. O. Hetmar *et al* 53–58
  Organic manic syndrome associated with advanced uraemia due to polycystic kidney disease. Christopher S. Thomas and T. James Neale (BR) 119–121
Koro. Drug-induced koro in a non-Chinese man. Eric Chen (C) 721
Kuru. "Life, Jim, but not as we know it?" Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts (*Review article*) 457–470

L-trytophan. Beyond pumpkin seeds. Shelagh Axford *et al* (C) 573
Late life *see* **Elderly**
Laterality. Early cortical tactile-evoked potentials, laterality and schizophrenia. Jane E. Allen *et al* 529–533
Lectures
  Eliot Slater Memorial 1990: Jealousy: the pathology of passion. Paul E. Mullen 593–601
  Maudsley 1990: Dangerous mistakes. Nigel Walker 752–757
Liaison services
  Child and psychiatry liaison services. L. McGibben and C. Ballard (C) 573
  Impact of a child psychiatry liaison service on patterns of referral. Anne McFadyen *et al* 93–96
Lifestyle. Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial. David Wheatley and C. Bass (*Current literature*) 264–267
Lithium
  Lithium maintenance: 1. A standard education programme for patients. Malcolm Peet and Norman S. Harvey 197–200
  Lithium maintenance: 2. Effects of personality and attitude on health information acquisition and compliance. Norman S. Harvey and Malcolm Peet 200–204
  Lithium treatment and prophylaxis in unipolar depression, a meta-analysis. F. G. M. Souza and G. M. Goodwin 666–675
  Long-term effects on the kidney. A prospective follow-up study ten years after kidney biopsy. O. Hetmar *et al* 53–58
  Prophylactic lithium in puerperal psychosis. The experience of three centres. D. E. Stewart *et al* 393–397
  Recording of information in case notes. D. L. F. Dunleavy and P. L. Cornwall (C) 571
Long-stay patients
  Nature and severity of disabilities in long-stay psychiatric in-patients in South Glamorgan. I. G. Pryce *et al* 817–821
  Social networks of long-term patients. David Abrahamson (C) 718–719

Lorazepam. Double-blind comparison of the effects of gradual withdrawal of lorazapam, diazepam and bromazepam in benzodiazepine dependence. Siobhan M. Murphy and Peter Tyrer 511–516

Magnetic resonance imaging. MRI study of schizophrenia. Brain structure and clinical symptoms. A. H. Young *et al* 158–164

Mania
- Buspirone-induced mania. Ronan J. McIvor and Kenneth Sinanan (C) 136–137
- Organic manic syndrome associated with advanced uraemia due to polycystic kidney disease. Christopher S. Thomas and T. James Neale (BR) 119–121
- Selection of controls. Ian Gale (C) 862. Rodney Morice (C) 862–863
- Spontaneous improvement of tardive dystonia during mania. O. Yazici *et al* (BR) 847–850
- Uraemia and mania. Franco Benazzi (C) 718

Manic depression. No evidence for a susceptibility locus predisposing to manic depression in the region of the dopamine (D2) receptor gene. Deborah Holmes *et al* 635–641

Marital and family psychotherapy. Robin Skynner: *One Flesh: Separate Persons.* Stan Ruszcynski (*Books reconsidered*) 868–870

Marital quality. Modes of relating, marital quality and depression. John Birtchnell 648–657

Medical Research Council. Molecular genetics of the major psychoses. The role of the Medical Research Council. D. A. Rees and Katherine Levy (*Molecular biology symposium*) 602–604

Men
- Berkeley Group. David A. G. Cook *et al* 238–243
- Depression and previous alcoholism in the elderly. Brian L. Cook *et al* 72–75

Menopause. Depression and the menopause. David Wheatley (C) 431–432, Ernest H. Friedman (C) 432, Louis Appleby (C) 864–865

Mental disorders *see* **Psychiatric disorders**

Mental handicap
- *Complications*
  - Assessing schizophrenia in adults with mental retardation. A comparative study. G. Meadows *et al* 103–105
  - Depression-dependent erotomanic delusions in a mentally handicapped woman. M. Ghaziuddin and L. Tsai (BR) 127–129
  - Motor disorders of mental handicap. An overlap with the motor disorders of severe psychiatric illness. D. Rogers *et al* 97–102
  - Motor disorders of the mentally handicapped. D. Kohen and G. Mathew (C) 571
  - Polydipsia and water intoxication in a mental handicap hospital. Alexander J. Bremner and Adrienne Regan 244–250
  - Systemic lupus erythematosus in a woman with mental handicap. David N. Wilson (BR) 427–429
- *Therapy*
  - Prescribing in mental handicap hospitals. T. W. Fan (C) 282–283, Stephen Tyrer *et al* 283
  - Psychiatric symptoms, diagnoses and care needs of 100 mentally handicapped patients. Brian R. Ballinger *et al* 251–254

Mental Health Act 1983. Compulsory psychiatric treatment in the community. I. Controlled study of compulsory community treatment with extended leave under the Mental Health Act: special characteristics of patients treated and impact of treatment. Tom Sensky *et al* 792–799

Mental retardation *see* **Mental handicap**

Meta-analysis. Lithium treatment and prophylaxis in unipolar depression, a meta-analysis. F. G. M. Souza and G. M. Goodwin 666–675

Methadone. Comparison of the withdrawal responses of heroin and methadone addicts during detoxification. Michael Gossop and John Strang 697–699

Middle East. Gilles de la Tourette syndrome in the Middle East. Report of a cohort and a multiply affected large pedigree. Mary M. Robertson and M. R. Trimble (BR) 416–419

Minkowski, E. *La Schizophrènie.* (John Cutting) (*Books reconsidered*) 293–295

Models
- Distiction of positive and negative symptoms. The failure of a two-dimensional model. Stephan Arndt *et al* 317–322
- Genetic model compatible with a dimensional view of schizophrenia. David Roberts and Gordon Claridge (*Annotation*) 451–456
- Social deprivation and rates of treated mental disorder. Developing statistical models to predict psychiatric service utilisation. Graham Thornicroft 475–484

Modes of relating. Negative modes of relating, marital quality and depression. John Birtchnell 648–657

Molecular biology symposium
- Collaborative strategies in the molecular genetics of the major psychoses. Marion Leboyer and Peter McGuffin 605–610
- Genetics of schizophrenia is the genetics of neurodevelopment. Peter Jones and Robin M. Murray 615–623
- Molecular genetics of the major psychoses. The role of the Medical Research Council. D. A. Rees and Katherine Levy 602–604
- Search for the psychosis gene. T. J. Crow 611–614

Monoamine oxidase inhibitors. Dependence on monoamine oxidase inhibitors in high dose. Dimitrios Vartzopoulos and Friedrich Krull (BR) 856–857

Mood disorders *see* **Affective disorders**

Morgan–Russell scales. Anorexia nervosa: outcome and prognostic factors after 20 years. R. H. Ratnasuriya *et al* 495–502

Mother–child interaction. Relationship with post-natal depression. Alan Stein *et al* 46–52

Motor disorders
- Motor disorders of mental handicap. An overlap with the motor disorders of severe psychiatric illness. D. Rogers *et al* 97–102
- Motor disorders of the mentally handicapped. D. Kohen and G. Mathew (C) 571

Multiple sclerosis. Hypersexuality, fetishism and multiple sclerosis. R. Huws *et al* (BR) 280–281

Music. Music as a remedy. Henry Rollin (*A hundred years ago*) 578

Neurodevelopment. Genetics of schizophrenia is the genetics of neurodevelopment. Peter Jones and Robin M. Murray (*Molecular biology symposium*) 615–623

Neuroleptic malignant syndrome (NMS)
  Carbamazepine and NMS. Fiona Coulter and F. M. Corrigan (C) 434–435
  Catatonia: harbinger of the neuroleptic malignant syndrome. Denise A. C. White and Ashley H. Robins (BR) 419–421
  Catatonia and NMS. T. K. S. Tan and S. H. Ong (C) 858, Denise A. C. White and Ashley H. Robins (C) 858–859, Tim Dalkin and Jo Kennedy (C) 859
  Clozapine-treated NMS. M. F. Burrell *et al* (C) 577
  CPK in NMS. Bridget Craddock *et al* (C) 130
  Is the predisposition to neuroleptic malignant syndrome genetically determined? Koichi Otani *et al* (BR) 850–853
  Myth of serum creatinine phosphokinase level and neuroleptic malignant syndrome. Adityanjee (*Point of view*) 706–707

Neuroleptics
  Facial dyskinesia: a 16-year follow-up study. H. A. McClelland *et al* 691–696
  Pisa syndrome in an adolescent on neuroleptic medication. Jeremy Turk and Bryan Lask (BR) 419–421
  Prediction of chronic persistent versus intermittent tardive dyskinesia. A retrospective follow-up study. William M. Glazer *et al* 822–828

Neurological soft signs
  Clinical correlates of neurological soft signs in chronic schizophrenia. D. J. King *et al* 770–775
  Educational status and neurological abnormalities in schizophrenia. K. S. Shaji (C) 865–866

Neuropeptides. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, β-endorphin and somatostatin. Charles B. Nemeroff *et al* 59–63

Neuroses. Care of chronic neurotic out-patients by community psychiatric nurses. A long-term follow-up study. Tom Burns *et al* 685–690

'New long-stay patients'. Planning for community care. Long-stay populations of hospitals scheduled for rundown or closure. P. Clifford *et al* 190–196

Nigeria. Interictal psychopathology in epilepsy. Prevalence and pattern in a Nigerian clinic. Oye Gureje 700–705

Nithsdale schizophrenia surveys. VIII: Do relatives want family intervention – and does it help? R. G. McCreadie *et al* (BR) 110–113

Nursing. Nursing of the insane. Henry Rollin (*A hundred years ago*) 722

Obsessive–compulsive disorder (OCD)
  Gender-divergent aetiological factors in obsessive–compulsive disorder. Homa F. Noshirvani *et al* 260–263
  In-patient behavioural psychotherapy unit. Description and audit. Graham Thornicroft *et al* 362–367
  Pattern of obsessive–compulsive disorder in Eastern Saudi Arabia. Osama Mohamed Mahgoub and Hassan Babiker Abdel-Hafeiz (BR) 840–842
  Tardive oculogyric crisis and obsessional thoughts. Perminder Sachdev (C) 720–721

Old age *see* **Elderly**

Oncogenes. Functional psychoses – are oncogenes involved in their pathogenesis? Some speculations. John Leach (*Point of view*) 563–568

One Flesh: Separate Persons. Robin Skynner (Stan Ruszczynski) (*Books reconsidered*) 868–870

Out-patients
  Care of chronic neurotic out-patients by community psychiatric nurses. A long-term follow-up study. Tom Burns *et al* 685–690
  Controlled comparison of day-patient and out-patient treatment for persistent anxiety and depression. Peter H. Dick *et al* 24–27

Panic disorders
  Panic attacks in schizophrenia. Luis M. Iruela *et al* (C) 436–437
  Pituitary microadenoma presenting as panic attacks. James Allen Wilcox (BR) 426–427

Paradigms
  Comment on the Modified Rogers Scale and the 'conflict of paradigms' hypothesis. Peter F. Liddle 337–339
  Motor, volitional disorders in schizophrenia. 2: 'conflict of paradigms' hypothesis. P. J. McKenna *et al* 328–336

Paraphilic coercive disorder. Successful treatment of paraphilic coercive disorder (a rapist) with fluoxetine hydrochloride. Martin P. Kafka (BR) 844–847

Parasuicide. Monthly and seasonal variation in parasuicide. A sex difference. George Masterton 155–157

Parietal lobes
  Dementia with parietal signs. Carrick McDonald (C) 859, Ronan O'Carroll (C) 859–860
  Parietal signs and sinister prognosis in dementia. A four-year follow-up study. Ronan O'Carroll *et al* 358–361

Parity. Gender, parity and the prevalence of minor affective disorder. P. E. Bebbington *et al* 40–45

Paroxetine. No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine. Bengt-O. Bengtsson *et al* (BR) 853–855

Physostigmine
  Cerebral pharmacodynamics of physostigmine in Alzheimer's disease investigated using single-photon computerised tomography. R. Hunter *et al* 351–357
  Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. Ken Wilson *et al* (*Current literature*) 558–562

Pisa syndrome. Pisa syndrome in an adolescent on neuroleptic medication. Jeremy Turk and Bryan Lask (BR) 422–423

Pituitary tumours. Pituitary microadenoma presenting as panic attacks. James Allen Wilcox (BR) 426–427

Plasma levels. Plasma levels of fluphenazine in patients receiving fluphenazine decanoate. Relationship to clinical response. Stephen R. Marder *et al* 658–665
Points of view
Classification and treatment of dysthymia. D. G. M. Murphy 106–109
Functional psychoses – are oncogenes involved in their pathogenesis? Some speculations. John Leach 563–568
Myth of serum creatinine phosphokinase level and neuroleptic malignant syndrome. Adityanjee 706–707
Polycythaemia rubra vera. Polycythaemia rubra vera, cerebral ischaemia and depression. Declan Murray and Richard Hodgson (BR) 842–844
Polydipsia
Intoxication by water. Alexander J. Bremner and Adrienne Regan 244–250
Vasopressin in polydipsia. Morris B. Goldman (C) 569, N. J. Delva *et al* (C) 570
Positron emission tomography (PET). Estimated density of D_2 striatal receptors in schizophrenia. A study with positron emission tomography and ^{76}Br-bromolisuride. J. L. Martinot *et al* 346–350
Post-traumatic stress disorder. Exposure therapy for post-traumatic stress disorder. Four case studies. David A. Richards and John S. Rose (BR) 836–840
Potentials
Auditory selective attention and event-related potentials in schizophrenia. Philip B. Ward *et al* 534–539
Early cortical tactile-evoked potentials, laterality and schizophrenia. Jane E. Allen *et al* 529–533
Pre-school Behaviour Checklist (PBCL). Behaviour disorder in Hong Kong pre-school children. Siu-Luen Luk *et al* 213–221
Prescription-event monitoring (PEM). Prescription-event monitoring of 10 895 patients treated with alprazolam. J. Guy Edwards *et al* 387–392
Primitive reflexes. Primitive reflexes in Alzheimer's disease. Paul Crichton and Carrick McDonald (C) 436
Processing negativity. Auditory selective attention and event-related potentials in schizophrenia. Philip B. Ward *et al* 534–539
Progressive supranuclear palsy. Neuropsychiatric evolution of a case. Sing Lee (BR) 273–275
Prosecution. Treatment as an alternative to prosecution: offenders diverted to treatment. David J. Cooke 785–791
Proteins. 'Life, Jim, but not as we know it?' Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts (*Review article*) 457–470
Psychiatric disorders
Classification
Comparison of CATEGO-derived ICD–8 and DSM–III. Classifications using the Composite International Diagnostic Interview in severely ill subjects. Anne E. Farmer *et al* 177–182
Social order/mental disorder. John Crammer (C) 430–431
Complications
Motor disorders of mental handicap. An overlap with the motor disorders of severe psychiatric illness. D. Rogers *et al* 97–102
Prevalence of delusional jealousy in different psychiatric disorders. An analysis of 93 cases. M. Soyka *et al* 549–553
Psychiatric diagnoses in ulcerative colitis. A controlled study. G. Magni *et al* (BR) 413–415
Incidence
Survey of psychiatrically ill Asian children. Syed Hasan Jawed (BR) 268–270
Using the Hospital and Anxiety and Depression scale to screen for psychiatric disorders in people presenting with deliberate self-harm. D. Hamer *et al* 782–784
Physiopathology. Urinary chromatographic profiles in psychiatric diseases. J. J. Gilroy *et al* (C) 288–289
Psychopathology
Incestuous abuse in psychiatric patients. Johann Kinzl and Wilfried Biebl (C) 719
Longitudinal study of psychological and social factors affecting recovery from psychiatric breakdowns. Keith Oatley and Christina Perring 28–32
Therapy
Randomised controlled trial of day and in-patient psychiatric treatment. 2: Comparison of two hospitals. Francis Creed *et al* 183–189
Replacing the mental hospital. Community provision for a district's chronically disabled in domestic environments? David Kingdon *et al* (BR) 113–117
Social deprivation and rates of treated mental disorder. Developing statistical models to predict psychiatric service utilisation. Graham Thornicroft 475–484
see also **Psychoses**
Psychiatric screening. Psychiatric screening of admissions to an accident and emergency ward. Gary Bell *et al* 554–557
Psychiatrists
Educating the psychiatrist of the 21st century. Harold Bourne (C) 137–138
Ethnic minorities and the psychiatric system. Roland Littlewood (C) 433–434
Racism and psychiatry. Glyn Lewis and Anthony David (C) 432–433
Psychodynamics
Psychoanalysis and psychotic depression. Charles Lund 523–528
Self-esteem as a factor in social and domestic violence. Ismond Rosen 18–23
Psychoses
Complications
Psychosis following hydatidiform mole in a patient with recurrent puerperal psychosis. S. W. Hopker and I. F. Brockington (BR) 122–123
Psychotic depression presenting as status epilepticus. Jean Claude Monfort and Andre Manus (C) 570–571
Steroid stupor in a surgical ward. M. Doherty *et al* (BR) 125–127
Genetics
Collaborative strategies in the molecular genetics of the major psychoses. Marion Leboyer and Peter McGuffin (*Molecular biology symposium*) 605–610

Molecular genetics of the major psychoses. The role of the Medical Research Council. D. A. Rees and Katherine Levy (*Molecular biology symposium*) 602–604
Search for the psychosis gene. T. J. Crow (*Molecular biology symposium*) 611–614
Pathology
Brain lesions and cognitive function in late-life psychosis. Bruce L. Miller *et al* 76–82, Alistair Flint *et al* (C) 866
Functional psychoses – are oncogenes involved in their pathogenesis? Some speculations. John Leach (*Point of view*) 563–568
Psychopathology
Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis. Alice Foerster *et al* 171–176
Psychotic depression: psychoanalytic psychopathology in relation to treatment and management. Charles Lund 523–528
Stress and puerperal psychosis. T. Kitamura *et al* (C) 290–291
Therapy
Management of first episode psychotic illness in Afro-Caribbean patients. Eric Y. H. Chen *et al* 517–522
Prophylactic lithium in puerperal psychosis. The experience of three centres. D. E. Stewart *et al* 393–397
Toluene-related psychosis. Alan Byrne and Terry Zibin (C) 578
Verapamil in major (psychotic) depression. Raymond M. Jacques and Stephen J. Cox (BR) 124–125

Psychosocial factors
Adversity in groups with an increased risk of minor affective disorder. P. E. Bebbington *et al* 33–40
Longitudinal study of psychological and social factors affecting recovery from psychiatric breakdowns. Keith Oatley and Christina Perring 28–32

Psychotherapy
On Becoming a Person: A Therapist's View of Psychotherapy. Carl Ransom Rogers (Duncan Cramer) (*Books reconsidered*) 139–141
see also **Behaviour, Group psychotherapy,** and **Marital and family psychotherapy**

Puerperium
Prophylactic lithium in puerperal psychosis. The experience of three centres. D. E. Stewart *et al* 393–397
Psychosis following hydatidiform mole in a patient with recurrent puerperal psychosis. S. W. Hopker and I. F. Brockington (BR) 122–123
Stress and puerperal psychosis. T. Kitamura *et al* (C) 290–291

Pumpkin seeds. Beyond pumpkin seeds. Shelagh Axford *et al* (C) 573

Questionnaires
Behaviour Screening Questionnaire (BSQ): Behaviour disorder in Hong Kong pre-school children. Siu-Luen Luk *et al* 213–221
Body Shape Questionnaire (BSQ): Eating disorders among Asian schoolgirls. D. R. Mumford *et al* 222–228
General Health Questionnaire (GHQ)
Psychiatric screening of admissions to an accident and emergency ward. Gary Bell *et al* 554–557
The GHQ and the HAD. R. P. Snaith (C) 433
Goodmayes Network Analysis Questionnaire (GNAQ). Social networks of long-term patients. David Abrahamson (C) 718–719

Racism
Are British psychiatrists racist? Roland Littlewood (C) 135
Ethnic minorities and the psychiatric system. Roland Littlewood (C) 433–434
Racial stereotypes. Suman Fernando (C) 289–290
Racism and psychiatry. Glyn Lewis and Anthony David (C) 432–433

Reading about...
Group psychotherapy. Michael Hobbs 723–725
Postgraduate psychiatry. Louis Appleby 439–431
Transcultural psychiatry. John L. Cox 579–582

Referrals. Impact of a child psychiatry liaison service on patterns of referral. Anne McFadyen *et al* 93–96

Relatives
Changes in patient coping style following individual and family treatment for schizophrenia. Margaret M. Rea *et al* 642–647
Engagement of relatives in intervention programmes. Julian Leff *et al* (C) 571–572

Restraint. The non-restraint question. Henry Rollin. (*A hundred years ago*) 292

Review articles
Child psychiatry in developing countries. Anula D. Nikapota 743–751
"Life, Jim, but not as we know it?" Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts 457–470
Schizophrenia: a neuropathological perspective. G. W. Roberts 8–17

Rogers scale
Commentary on the modified Rogers scale and the 'conflict of paradigms' hypothesis. Peter F. Liddle 337–339
Motor, volitional and behavioural disorders in schizophrenia. 1: Assessment using the modified Rogers scale. C. E. Lund *et al* 323–327

Sarcoidosis. Bipolar disorder and cerebral sarcoidosis. Declan McLoughlin and Patrick McKeon (BR) 410–413

Saudi Arabia. Pattern of obsessive–compulsive disorder in Eastern Saudi Arabia. Osama Mohammed Mahgoub and Hassan Babiker Abdel-Hafeiz (BR) 840–842

Scales
Assessment of positive and negative symptoms of schizophrenia (SAPS and SANS): Auditory selective attention and event-related potentials in schizophrenia. Philip B. Ward *et al* 534–539

Edinburgh Postnatal Depression Scale (EPDS). EPDS by post. Josephine M. Green *et al* (C) 865

Hamilton Rating Scale for Depression: Professor Max Hamilton: an apology. Peter A. van Keep (C) 434

Hospital Anxiety and Depression (HAD) scale. The GHQ and the HAD. R. P. Snaith (C) 433

Modified Rogers scale

Catatonic symptoms in schizophrenia. P. J. McKenna *et al* 328–336

Commentary on the conflict of paradigms hypothesis. Peter F. Liddle 337–339

Morgan-Russell scales. Anorexia nervosa: outcome and prognostic factors after 20 years. R. H. Ratnasuriya *et al* 495–502

Using the Hospital and Anxiety and Depression scale to screen for psychiatric disorders in people presenting with deliberate self-harm. D. Hamer *et al* 782–784

see also **Checklist, Inventory, Questionnaires, Schedules** and **Test**

Schedules

Diagnostic Interview schedule (DIS). Is sex necessarily a risk factor to depression? Tirril Harris *et al* (*Current literature*) 708–712

Schedule for Affective Disorders and Schizophrenia (SADS-L): Assessing schizophrenia in the mentally handicapped. G. Meadows *et al* 103–105

Social Network Schedule (SNS). Social networks of long-term patients. David Abrahamson (C) 718–719

Schizoaffective disorders. Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizoaffective disorders. Ming T. Tsuang 165–170

Schizophrenia

Complications

Assessing schizophrenia in adults with mental retardation. A comparative study. G. Meadows *et al* 103–105

Panic attacks in schizophrenia. Luis M. Iruela *et al* (C) 436–437

Family. Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizoaffective disorders. Ming T. Tsuang 165–170

Genetics

Evidence for a pseudo-autosomal locus for schizophrenia using the method of affected sibling pairs 624–629

Genetic model compatible with a dimensional view of schizophrenia. David Roberts and Gordon Claridge (*Annotation*) 451–456

Genetics of schizophrenia is the genetics of neurodevelopment. Peter Jones and Robin M. Murray (*Molecular biology symposium*) 615–623

No genetic linkage detected for schizophrenia to Xq27–q28. Lynn E. Delisi *et al* 630–634

Incidence

Is schizophrenia disappearing? John M. Eagles (*Current literature*) 834–835

Season of birth in schizophrenia. Evidence for confinement of an excess of winter births to patients without a family history of mental disorder. Eadbhard O'Callaghan *et al* 764–769

Unexplained variations in the risk for schizophrenia by month and year of birth. R. E. Kendell and W. Adams 758–763

Pathology

Clinical correlates of neurological soft signs in chronic schizophrenia. D. J. King *et al* 770–775

Computerised tomography and schizophrenia. Robert Miller (C) 863

Educational status and neurological abnormalities in schizophrenia. K. S. Shaji (C) 865–866

MRI study of schizophrenia. Brain structure and clinical symptoms. A. H. Young *et al* 158–164

Neuropathological perspective. G. W. Roberts (*Review article*) 8–17

Physiopathology

Auditory selective attention and event-related potentials in schizophrenia. Philip B. Ward *et al* 534–539

Early cortical tactile-evoked potentials, laterality and schizophrenia. Jane E. Allen *et al* 529–533

Estimated density of D_2 striatal receptors in schizophrenia. A study with positron emission tomography and ^{76}Br-bromolisuride. J. L. Martinot *et al* 346–350

Human leucocyte antigens and tardive dyskinesia. K. W. Brown and T. White (BR) 270–272

Motor, volitional and behavioural disorders in schizophrenia

1: Assessment using the modified Rogers scale. C. E. Lund *et al* 323–327

2: 'Conflict of paradigms' hypothesis. P. J. McKenna *et al* 328–336

Prognosis. First episode schizophrenia predicting outcome. Matthijs Muijen (C) 713, Eve C. Johnstone *et al* (C) 713–714

Psychology

Changes in patient coping style following individual and family treatment for schizophrenia. Margaret M. Rea *et al* 642–647

Distinction of positive and negative symptoms. The failure of a two-dimensional model. Stephan Arndt *et al* 317–322

La Schizophrènie. E. Minkowski. (John Cutting) (*Books reconsidered*) 293–295

Nithsdale schizophrenia surveys. VIII: Do relatives want family intervention – and does it help? R. G. McCreadie *et al* (BR) 110–113

Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis. Alice Foerster *et al* 171–176

Schizophrenic symptoms and frontal lobe performance. Peter F. Liddle and Danielle L. Morris 340–345

Selection of controls. Ian Gale (C) 862, Rodney Morice (C) 862–863

Schizotypal disorders. Borderline and schizotypal disorders in children and adolescents. Martijn Meijer and Philip D. A. Treffers 205–212

Schoolgirls. Eating disorders among Asian schoolgirls. D. B. Mumford *et al* 222–228, Santosh K Chaturvidi (C) 860–861, David B. Mumford (C) 861

- **Scotland**
  - Scottish survey of old long-stay in-patients. R. G. McCreadie *et al* 398–402
  - Treatment as an alternative to prosecution: offenders diverted to treatment. David J. Cooke 785–791
- **Scull, Andrew.** *Museums of Madness.* Social order/mental disorder. John Crammer (C) 430–431
- **Season of birth**
  - Season of birth in schizophrenia. Evidence for confinement of an excess of winter births to patients without a family history of mental disorder. Eadbhard O'Callaghan *et al* 764–769
  - Unexplained variations in the risk for schizophrenia by month and year of birth. R. E. Kendell and W. Adams 758–763
- **Self-esteem.** A factor in social and domestic violence. Ismond Rosen 18–23
- **Self-harm**
  - Using the Hospital and Anxiety and Depression scale to screen for psychiatric disorders in people presenting with deliberate self-harm. D. Hamer *et al* 782–784
  - What happens to patients who frequently harm themselves? A retrospective one-year outcome study. Ruth Stocks and Allan I. F. Scott 375–378
- **Serum.** Myth of serum creatinine phosphokinase level and neuroleptic malignant syndrome. Adityanjee (*Point of view*) 706–707
- **Sex differences**
  - Is sex necessarily a risk factor to depression? Tirril Harris *et al* (*Current literature*) 708–712
  - Monthly and seasonal variation in parasuicide. A sex difference. George Masterton 155–157
  - Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis. Alice Foerster *et al* 171–176
  - Sex differences in suicidal behaviour of referred adolescents. Joseph M. Rey and Kevin D. Bird 776–81
  - *see also* **Gender, Men, Schoolgirls** and **Women**
- **Sex offenders.** Berkeley Group. Ten years' experience of a group for non-violent sex offenders. David A. G. Cook *et al* 238–243
- **Single-photon emission computerised tomography (SPECT)**
  - Cerebral pharmacodynamics of physostigmine in Alzheimer's disease investigated using single-photon computerised tomography. R. Hunter *et al* 351–357
  - Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. Ken Wilson *et al* (*Current literature*) 558–562
- **Skynner, Robin.** *One Flesh: Separate Persons.* Stan Ruszcynski (*Books reconsidered*) 868–870
- **Sleep disorders.** Confusions concerning sleep disorders and the epilepsies in children and adolescents. Gregory Stores (*Annotation*) 1–7
- **Social deprivation.** Social deprivation and rates of treated mental disorder. Developing statistical models to predict psychiatric service utilisation. Graham Thornicroft 475–484
- **Social Network Schedule (SNS).** Social networks of long-term patients. David Abrahamson (C) 718–719
- **Social order/mental disorder.** *Museums of Madness.* John Crammer (C) 430–431
- **Somatostatin,** Neuropeptide concentrations in CSF before and after ECT. Charles B. Nemeroff *et al* 59–63
- **South Glamorgan.** Nature and severity of disabilities in long-stay psychiatric in-patients in South Glamorgan. I. G. Pryce *et al* 817–821
- **Spongiform encephalopathies.** "Life, Jim, but not as we know it?" Transmissible dementias and the prion protein. Paul J. Harrison and Gareth W. Roberts (*Review article*) 457–470
- **Statistics**
  - First episode schizophrenia predicting outcome. Matthijs Muijen (C) 713, Eve C. Johnstone *et al* (C) 713–714
  - *see also* **Meta-analysis**
- **Stereotypes.** Racial stereotypes. Suman Fernando (C) 289–290
- **Steroids.** Steroid stupor in a surgical ward. M. Doherty *et al* (BR) 125–127
- **Stress**
  - Exposure therapy for post-traumatic stress disorder. Four case studies. David A. Richards and John H. Rose (BR) 836–840
  - Stress and puerperal psychosis. T. Kitamura *et al* (C) 290–291
- **Strokes.** Mood disorders in the year after first stroke. Allan House *et al* 83–92
- **Stupor.** Steroid stupor in a surgical ward. M. Doherty *et al* (BR) 125–127
- **Suicide**
  - Sex differences in suicidal behaviour of referred adolescents. Joseph M. Rey and Kevin D. Bird 776–81
  - Suicide in Indian women. R. K. Chadda *et al* (C) 434
  - Suicide and unexpected deaths among psychiatric in-patients. The Bristol confidential inquiry. H. G. Morgan and Pamela Priest 368–374
- **Systemic lupus erythematosus (SLE)**
  - SLE and multi-infarct dementia. B. M. Green and K. C. M. Wilson (C) 291–292
  - Systemic lupus erythematosus in a woman with mental handicap. David N. Wilson (BR) 427–429

- **Tardive dyskinesia**
  - Clinical correlates of neurological soft signs in chronic schizophrenia. D. J. King *et al* 770–775
  - Effects of clozapine on tardive dyskinesia. Jeffrey A. Liebermann *et al* 503–510
  - Human leucocyte antigens and tardive dyskinesia. K. W. Brown and T. White. (BR) 270–272
  - Prediction of chronic persistent versus intermittent tardive dyskinesia. A retrospective follow-up study. William M. Glazer *et al* 822–828
  - Tardive dyskinesia and HLA. Padraigh Wright (C) 863–864
- **Tardive dystonia.** Spontaneous improvement of tardive dystonia during mania. O. Yazici *et al* (BR) 847–850
- **Tardive oculogyric crisis.** Tardive oculogyric crisis and obsessional thoughts. Perminder Sachdev (C) 720–721
- **Television.** All-night television can damage your health. Robert Howard (C) 577–578
- **Temporal lobe: medial.** Schizophrenia: a neuropathological perspective. G. W. Roberts (*Review article*) 8–17

Test. Eating Attitudes Test (EAT). Eating disorders among Asian schoolgirls. D. R. Mumford *et al* 222–228

Thought disorder. Ordering thoughts on thought disorder. John McGrath 307–316

Tolbutamide. Tolbutamide and fatal water intoxication. Pritesh J. Shah and William M. Greenberg (C) 719–720

Toluene. Toluene-related psychosis. Alan Byrne and Terry Zibin (C) 578

Tolvon. Professor Max Hamilton: an apology. Peter A. van Keep (C) 434

Torture. Psychological sequelae of torture. Dora Kohen (C) 287

Tourette syndrome. Gilles de la Tourette syndrome in the Middle East. Report of a cohort and a multiply affected large pedigree. Mary M. Robertson and M. R. Trimble (BR) 416–419

Training

- Is psychiatric training still improving? T. K. S. Tan and M. Elnesr (C) 134–135
- Postgraduate psychiatry. Louis Appleby (*Reading about...*) 439–431

Transsexualism. R. P. Snaith *et al* (C) 132–133

Trazodone. Trazodone-induced transient hypomanic symptoms and their management. S. Jabeen and C. J. Fisher (BR) 275–278

Treatment compliance

- Compulsory psychiatric treatment in the community
  - I. Controlled study of compulsory community treatment with extended leave under the Mental Health Act: special characteristics of patients treated and impact of treatment. Tom Sensky *et al* 792–799
  - II. Controlled study of patients whom psychiatrists would recommend for compulsory treatment in the community. Tom Sensky *et al* 799–804

Ulcerative colitis. Psychiatric diagnoses in ulcerative colitis. A controlled study. G. Magni *et al* (BR) 413–415

Unemployment. First episode schizophrenia predicting outcome. Matthijs Muijen (C) 713, Eve C. Johnstone *et al* (C) 713–714

Unfit to plead. Unfit to plead in England and Wales, 1976–88. A survey. D. H. Grubin 540–548

Uraemia

- Mania, uraemia and kidney disease. Christopher S. Thomas and T. James Neale (BR) 119–121
- Uraemia and mania. Franco Benazzi (C) 718

Urine. Urinary chromatographic profiles in psychiatric diseases. J. J. Gilroy *et al* (C) 288–289

Vasopressin. Vasopressin in polydipsia. Morris B. Goldman (C) 569, N. J. Delva *et al*. 570

Verapamil. Verapamil in major (psychotic) depression. Raymond M. Jacques and Stephen J. Cox (BR) 124–125

Violence. Self-esteem as a factor in social and domestic violence. Ismond Rosen 18–23

Water intoxication

- Polydipsia and water intoxication in a mental handicap hospital. Alexander J. Bremner and Adrienne Regan 244–250
- Tolbutamide and fatal water intoxication. Pritesh J. Shah and William M. Greenberg (C) 719–720

Withdrawal

- Benzodiazepine withdrawal syndrome. Malcolm Lader and Sally Morton (C) 435–436
- Comparison of the withdrawal responses of heroin and methadone addicts during detoxification. Michael Gossop and John Strang 697–699

Women

- Eating disorders in Asian women. Sing Lee (C) 131–132
- Gender, parity and the prevalence of minor affective disorder. P. E. Bebbington *et al* 40–45
- Gender-divergent aetiological factors in OCD. Homa F. Noshirvani *et al* 260–263
- Is sex necessarily a risk factor to depression? Tirril Harris *et al* (*Current literature*) 708–712
- Psychosis following hydatidiform mole. S. W. Hopker and I. F. Brockington (BR) 122–123
- Suicide in Indian women. R. K. Chadda *et al* (C) 434
- *see also* **Childbirth, Menopause** and **Puerperium**

Zimeldine. No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine. Bengt-O. Bengtsson *et al* (BR) 853–855

PART II. CONTRIBUTORS

Abdel-Hafeiz, Hassan Babiker *see* **Mahgoub, Osama Mohammed** (BR) 840–842

Abrahamson, David. Social networks of long-term patients (C) 718–719

Adams, Alison *see* **Axford, Shelagh** *et al* (C) 573

Adams, W. *see* **Kendell, R. E.** 758–763

Adityanjee. Myth of serum creatinine phosphokinase level and neuroleptic malignant syndrome. (*Point of view*) 706–707

Adityanjee *et al*. Diazepam abreaction (C) 289

Akil, Huda *see* **Nemeroff, Charles B.** *et al* 59–63

Allen, Jane E. *et al*. Early cortical tactile-evoked potentials, laterality and schizophrenia 529–533

Alliger, Randall J. *see* **Arndt, Stephan** *et al* 317–322

Allilaire, J. F. *see* **Martinot, J. L.** *et al* 346–350

Altham, Patricia *see* **Goodyer, Ian** *et al* 676–684

Anderson, D. N. and **Phaterpekar, H.** Demand for psychogeriatric services (C) 574–575

Andreasen, Nancy C. *see* **Arndt, Stephan** *et al* 317–322

Anthony, Phil *see* **Creed, Francis** *et al* 183–189

Appleby, Louis. Menopausal depression (C) 864–865

Appleby, Louis. Postgraduate psychiatry. (*Reading about*) 439–431

Aravagiri, Manickam *see* **Marder, Stephen R.** *et al* 658–665

Arndt, Stephan *et al*. Distinction of positive and negative symptoms. The failure of a two-dimensional model 317–322

Arnold, Elaine *see* **Cosford, Paul** (C) 286–287

Arya, Dinesh K. Anorexia nervosa across cultures (C) 285–286

Ashton, C. H. *et al.* Buspirone in benzodiazepine withdrawal (C) 283–284
Axford, Shelagh *et al.* Beyond pumpkin seeds (C) 573
Azevedo, M. H. Pinto de and **Moniz, Margarida**. Dystonia – a potential psychiatric pitfall (C) 436

Bacon-Shone, John *see* **Luk, Siu-Luen** *et al* 213–221
Baikie, Elizabeth *see* **O'Carroll, Ronan** *et al* 358–361
Baird, D. *see* **McCreadie, R. G.** *et al* (BR) 110–113
Balaraju, K. B. *see* **Adityanjee** *et al* (C) 289
Ballard, C. G. *et al.* Carbamazepine in alcohol withdrawal (C) 133
Ballard, C. G. *see* **McGibbon, Lawrence** *et al* (C) 285
Ballard, C. *see* **McGibben, L.** (C) 573
Ballinger, Brian R. *et al.* Psychiatric symptoms, diagnoses and care needs of 100 mentally handicapped patients 251–254
Ballinger, C. Barbara *see* **Ballinger, Brian R.** *et al* 251–254
Bamrah, J. S. and **Johnson, J.** Bipolar affective disorder following head injury (BR) 117–119
Bancroft, John *see* **Harris, Tirril** *et al.* (*Current literature*) 708–712
Barczak, P. *see* **Hamer, D.** *et al* 782–784
Bartlett, C. *see* **Rogers, D.** *et al* 97–102
Bass, C. *see* **Wheatley, David** (*Current literature*) 264–267
Bavington, J. T. *see* **Mumford, D. B.** *et al* 379–386
Beach, Vickie *see* **Cook, Brian L.** *et al* 72–75
Beaman, Katja *see* **Domb, Yair** (BR) 423–425
Beaufils, B. *see* **Martinot, J. L.** *et al* 346–350
Bebbington, P. E. *et al.* Adversity in groups with an increased risk of minor affective disorder 33–40
Bebbington, P. E. *et al.* Gender, parity and the prevalence of minor affective disorder 40–45
Bell, Gary *et al.* Psychiatric screening of admissions to an accident and emergency ward 554–557
Benazzi, Franco. Uraemia and mania (C) 718
Bengtsson, Bengt-O. *et al.* No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine (BR) 853–855
Bernasconi, G. *see* **Magni, G.** *et al* (BR) 413–415
Berney, Tom P. *see* **Tyrer, Stephen** *et al* (C) 283
Best, S. *see* **Clifford, P.** *et al* 190–196
Bhat, A. V. *see* **Lacey, J. Hubert** *et al* 491–494
Bhatia, M. S. *see* **Chadda, R. K.** *et al* (C) 434
Bhatnagar, K. S. *see* **Mumford, D. B.** *et al* 379–386
Biebl, Wilfred *see* **Kinzl, Johann** (C) 719
Biggins, C. A. *see* **McKenna, P. J.** *et al* 328–336
Birch, Jim. Family intervention (C) 717–718
Bird, Kevin D. *see* **Rey, Joseph M.** 776–81
Birtchnell, John. Negative modes of relating, marital quality and depression 648–657
Bissette, Garth *see* **Nemeroff, Charles B.** *et al* 59–63
Black, Dawn *see* **Creed, Francis** *et al* 183–189
Black, Dora *see* **McFadyen, Anne** *et al* 93–96
Blackwood, D. H. R. *see* **Young, A. H.** *et al* 158–164
Bliss, Judith *see* **Moorey, Stirling** *et al* 255–259
Boccio, A. *see* **Collinge, J.** *et al* 624–629
Boccio, Angela *see* **Delisi, Lynn E.** *et al* 630–634
Bolwig, T. G. *see* **Hetmar, O.** *et al* 53–58
Bond, Alison *see* **Stein, Alan** *et al* 46–52
Boone, Kyle B. *see* **Miller, Bruce L.** *et al* 76–82
Borenstein, Michael *see* **Lieberman, Jeffrey A.** *et al* 503–510
Bose, Michael J. von and **Zaudig, Michael**. Encephalopathy resembling Creutzfeldt–Jakob disease following oral, prescribed doses of bismuth nitrate (BR) 278–280
Bourne, Harold. Educating the psychiatrist of the 21st century (C) 137–138
Bowen, David *see* **Wilson, Ken** *et al* (*Current literature*) 558–562
Bremner, Alexander J. and **Regan, Adrienne**. Polydipsia and water intoxication in a mental handicap hospital 244–250
Brett, Peter *see* **Holmes, Deborah** *et al* 635–641
Brockington, I. F. *see* **Hopker, S. W.** (BR) 122–123
Broeckhoven, Christine van *see* **Duijn, Cornelia M. van** *et al* 471–474
Bromham, D. R. *see* **Snaith, R. P.** *et al* (C) 132–133
Broster, Gillian *see* **McFadyen, Anne** *et al* 93–96
Brown, K. W. and **White, T.** Human leucocyte antigens and tardive dyskinesia (BR) 270–272
Bryant-Waugh, Rachel and **Lask, Bryan**. Anorexia nervosa in Asian children 229–233
Brynjolfsson, Jon *see* **Holmes, Deborah** *et al* 635–641
Bucher, Janet *see* **Stein, Alan** *et al* 46–52
Buckley, Peter *see* **O'Callaghan, Eadbhard** *et al* 764–769
Burns, Alistair *et al.* Gender-identity clinic patients (C) 715
Burns, Tom *et al.* Care of chronic neurotic out-patients by community psychiatric nurses. A long-term follow-up study 685–690
Burrell, M. F. *et al.* Clozapine-treated NMS (C) 577
Burvill, P. W. *et al.* Prognosis of depression in old age 64–71
Butterworth, E. *see* **Hamer, D.** *et al* 782–784
Byrne, Alan and **Zibin, Terry**. Toluene-related psychosis (C) 578
Byrne, Patrick J. Patient data in child psychiatry (C) 572

Caballero, Luis *see* **Iruela, Luis M.** *et al* (C) 436–437
Campbell, L. *see* **Meadows, G.** *et al* 103–105
Canton, G. *see* **Magni, G.** *et al* (BR) 413–415
Cashman, M. *see* **Burrell, M. F.** *et al* (C) 577
Catts, Stanley V. *see* **Ward, Philip B.** *et al* 534–539
Chadda, R. K. *et al.* Suicide in Indian women (C) 434
Champney-Smith, J. *see* **Pryce, I. G.** *et al* 817–821
Chapman, M. *see* **Taranto, N. E. de** *et al* (C) 714–715
Charman, A. *see* **Clifford, P.** *et al* 190–196
Chaturvedi, Santosh K. Eating disorders in Asians (C) 860–861
Chen, Eric. Drug-induced koro in a non-Chinese man (C) 721
Chen, Eric Y. H. *et al.* Management of first episode psychotic illness in Afro-Caribbean patients 517–522
Chen, Sylvia *see* **Luk, Siu-Luen** *et al* 213–221
Christie-Brown, Jeremy *see* **Burns, Alistair** *et al* (C) 715
Chung, See-Yuen *see* **Luk, Siu-Luen** *et al* 213–221
Claridge, Gordon *see* **Roberts, David** (*Annotation*) 451–456

Clifford, P. *et al.* Planning for community care. Long-stay populations of hospitals scheduled for rundown or closure 190–196
Cohen, Samuel I. Erotomania in relation to childbirth (C) 291
Collinge, J. *et al.* Evidence for a pseudo-autosomal locus for schizophrenia using the method of affected sibling pairs 624–629
Collins, B. J. *see* **Doherty, M.** *et al* (BR) 125–127
Colohan, Hubert A. *see* **O'Callaghan, Eadbhard** *et al* 764–769
Colson, Louise *see* **Thornicroft, Graham** *et al* 362–367
Cook, Brian L. *et al.* Depression and previous alcoholism in the elderly 72–75
Cook, David A. G. *et al.* Berkeley Group. Ten years' experience of a group for non-violent sex offenders 238–243
Cooke, David J. Treatment as an alternative to prosecution: offenders diverted to treatment 785–791
Cooper, Peter J. *see* **Stein, Alan** *et al* 46–52
Cooper, S. J. *see* **King, D. J.** *et al* 770–775
Cornwall, P. L. *see* **Dunleavy, D. L. F.** (C) 571
Corrigan, F. M. *see* **Coulter, Fiona** (C) 434–435
Cosford, Paul and **Arnold, Elaine.** Anorexia in the elderly (C) 286–287
Coulter, Fiona and **Corrigan, F. M.** Carbamazepine and NMS (C) 434–435
Cox, John L. Transcultural psychiatry (*Reading about...*) 579–582
Cox, Stephen J. *see* **Jacques, Raymond M.** (BR) 124–125
Craddock, Bridget *et al.* CPK in NMS (C) 130
Craddock, Nick *see* **Craddock, Bridget** *et al* (C) 130
Crammer, J. L. *see* **Delva, N. J** *et al* (C) 570
Crammer, John. Social order/mental disorder (C) 430–431
Creed, Francis *et al.* Randomised controlled trial of day and in-patient psychiatric treatment. 2: Comparison of two hospitals 183–189
Crichton, Paul and **McDonald, Carrick.** Primitive reflexes in Alzheimer's disease (C) 436
Crombie, Iain K. *see* **Dick, Peter H.** *et al* 24–27
Crow, T. J. *see* **Gilroy, J. J.** *et al* (C) 288–289
Crow, T. J. Search for the psychosis gene (*Molecular biology symposium*) 611–614
Crow, T. J. *see* **Collinge, J.** *et al* 624–629
Crow, T. J. *see* **Johnstone, Eve C.** *et al* (C) 713–714
Crow, Timothy *see* **Delisi, Lynn E.** *et al* 630–634
Curtis, David *see* **Holmes, Deborah** *et al* 635–641
Cutting, John. *La Schizophrènie.* E. Minkowski (*Books reconsidered*) 293–295

Dalkin, Tim and **Kennedy, Jo.** Catatonia and NMS (C) 859
David, Anthony *see* **Lewis, Glyn** (C) 432–433
Davies, Kay E. *see* **Delisi, Lynn E.** *et al* 630–634
Day, Ann *see* **Stein, Alan** *et al* 46–52
Dean, C. *see* **Bebbington, P. E.** *et al* 40–45
Delisi, L. E. *see* **Collinge, J.** *et al* 624–629
Delisi, Lynn E. *et al.* No genetic linkage detected for schizophrenia to Xq27–q28. 630–634
Delva, N. J *et al.* Vasopressin in polydipsia (C) 570
Dennis, Martin *see* **House, Allan** *et al* 83–92
Der, G. *see* **Bebbington, P. E.** *et al* 40–45
Dick, Peter H. *et al.* Controlled comparison of day-patient and out-patient treatment for persistent anxiety and depression 24–27
Dingwall, J. M. *see* **McCreadie, R. G.** *et al* 398–402
D'Odorico, A. *see* **Magni, G.** *et al* (BR) 413–415
Doherty, M. *et al.* Steroid stupor in a surgical ward (BR) 125–127
Domb, Yair and **Beaman, Katja.** Mr X – a case of amnesia (BR) 423–425
Donnelly, J. *see* **Snaith, R. P.** *et al* (C) 132–133
Double, Duncan. Blinding trials (C) 573–574
Doucette, John T. *see* **Glazer, William M.** *et al* 822–828
Duggan, Conor F. *see* **Lee, Alan S.** (C) 287–288
Duijn, Cornelia M. van *et al.* Evidence for allelic heterogeneity in familial early-onset Alzheimer's disease 471–474
Dunleavy, D. L. F. and **Cornwall, P. L.** Recording of information in case notes (C) 571
Dutta, D. *see* **McClelland, H. A.** *et al* 691–696

Eagles, John M. Is schizophrenia disappearing? (*Current literature*) 834–835
Eastwood, Robin *see* **Flint, Alastair** (C) 866
Edwards, Griffith. Who was Jellinek? (C) 431
Edwards, J. Guy *et al.* Prescription-event monitoring of 10 895 patients treated with alprazolam 387–392
Eisler, I. *see* **Ratnasuriya, R. H.** *et al* 495–502
Elnesr, M. *see* **Tan, T. K. S.** (C) 134–135
Elsworth, E. *see* **Taranto, N. E. de** *et al* (C) 714–715
Emmerson, J. P. *see* **Burvill, P. W.** *et al* 64–71
Evans, Jonathan. Culture as a confounding variable (C) 133
Ezekiel, A. *see* **Burns, Tom** *et al* 685–690

Falloon, Ian *see* **Rea, Margaret M.** *et al* 642–647
Fan, T. W. Prescribing in mental handicap hospitals (C) 282–283
Farmer, Anne E. *et al.* Comparison of CATEGO-derived ICD–8 and DSM–III. Classifications using the Composite International Diagnostic Interview in severely ill subjects 177–182
Farrell, Michael *see* **Burns, Alistair** *et al* (C) 715
Fernando, Suman. Racial stereotypes (C) 289–290
Ferrier, I. N. *see* **Gilroy, J. J.** *et al* (C) 288–289
Fewster, C. *see* **Burrell, M. F.** *et al* (C) 577
Fink, Max *see* **Nemeroff, Charles B.** *et al* 59–63
Fisher, C. J. *see* **Jabeen, S.** (BR) 275–278
Flint, Alastair *et al.* Brain lesions and cognitive function in late-life psychosis (C) 866
Flint, Tracey *see* **Delisi, Lynn E.** *et al* 630–634
Flowers, P. *see* **Taranto, N. E. de** *et al* (C) 714–715
Foerster, Alice *et al.* Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis 171–176
Fox, Allison M. *see* **Ward, Philip B.** *et al* 534–539
Fox, Charles A. *see* **Cook, David A. G.** *et al* 238–243
Francis, Paul *see* **Wilson, Ken** *et al* (*Current literature*) 558–562
Franks, David *see* **Creed, Francis** *et al* 183–189

Friedman, Ernest H. Depression and the menopause (C) 432

Frith, C. D. *see* **Johnstone, Eve C.** *et al* (C) 714

Fukushima, Yutaka *see* **Otani, Koichi** *et al* (BR) 847–850

Gale, Ian. Selection of controls (C) 862

Garstin, I. *see* **Doherty, M.** *et al* (BR) 125–127

Garvey, J. *see* **Cook, Brian L.** *et al* 72–75

Gath, Dennis H. *see* **Stein, Alan** *et al* 46–52

Gentry, R. M. *see* **Pryce, I. G.** *et al* 817–821

Germany, Elizabeth *see* Goodyer, **Ian** *et al* 676–684

Ghaziuddin, M. and **Tsai, L.** Depression-dependent erotomanic delusions in a mentally handicapped woman (BR) 127–129

Gibson, Tessa *see* **O'Callaghan, Eadbhard** *et al* 764–769

Gillberg, Christopher *et al.* Is autism more common now than ten years ago? 403–409

Gilroy, J. J. *et al.* Urinary chromatographic profiles in psychiatric diseases. J. J. Gilroy *et al* (C) 288–289

Glazer, William M. *et al.* Prediction of chronic persistent versus intermittent tardive dyskinesia. A retrospective follow-up study 822–828

Goate, Alison M. *see* **Duijn, Cornelia M. van** *et al* 471–474

Goldman, Morris B. Vasopressin in polydipsia (C) 569

Goldstein, Michael J. *see* **Rea, Margaret M.** *et al* 642–647

Goodwin, G. M. *see* **Hunter, R.** *et al* 351–357

Goodwin, G. M. *see* **Souza, F. G. M.** 666–675

Goodyer, Ian *et al.* Social influences on the course of anxious and depressive disorders in school-age children 676–684

Gordon, A. G. Musical and verbal hallucinations (C) 715–716

Gorman, Christine *see* **Moorey, Stirling** *et al* 255–259

Gossop, Michael and **Strang, John.** Comparison of the withdrawal responses of heroin and methadone addicts during detoxification 697–699

Gowers, S. G. *see* **Lacey, J. Hubert** *et al* 491–494

Gowrusanker, Jaya *see* **Goodyer, Ian** *et al* 676–684

Green, B. M. and **Wilson, K. C. M.** SLE and multi-infarct dementia (C) 291–292

Green, Josephine M. *et al.* EPDS by post (C) 865

Greenberg, William M. *see* **Shah, Pritesh J.** (C) 719–720

Greer, Steven *see* **Moorey, Stirling** *et al* 255–259

Griffiths, R. D. *see* **Pryce, I. G.** *et al* 817–821

Grubin, D. H. Unfit to plead in England and Wales, 1976–88. A survey 540–548

Gureje, Oye. Interictal psychopathology in epilepsy. Prevalence and pattern in a Nigerian clinic 700–705

Gurling, Hugh *see* **Holmes, Deborah** *et al* 635–641

Hall, W. D. *see* **Burvill, P. W.** *et al* 64–71

Hambridge, Dave. Effects of belief on grief (C) 291

Hamer, D. *et al.* Using the Hospital and Anxiety and Depression scale to screen for psychiatric disorders in people presenting with deliberate self-harm 782–784

Handy, S. *see* **Ballard, C. G.** *et al* (C) 133

Handy, S. *see* **McGibbon, Lawrence** *et al* (C) 285

Hansen, M. T. *see* **Hunter, R.** *et al* 351–357

Hardy, John *see* **Duijn, Cornelia M. van** *et al* 471–474

Hardy, P. *see* **Martinot, J. L.** *et al* 346–350

Harris, Tirril *et al.* Is sex necessarily a risk factor to depression? (*Current literature*) 708–712

Harrison, Glynn *see* **Chen, Eric Y. H.** *et al* 517–522

Harrison, Paul J. and **Roberts, Gareth W.** 'Life, Jim, but not as we know it?' Transmissible dementias and the prion protein (*Review article*) 457–470

Harvey, J. A. *see* **McCreadie, R. G.** *et al* (BR) 110–113

Harvey, Norman S. and **Peet, Malcolm.** Lithium maintenance: 2. Effects of personality and attitude on health information acquisition and compliance 200–204

Harvey, Norman S. *see* **Peet, Malcolm** 197–200

Hawes, Edward M. *see* **Marder, Stephen R.** *et al* 658–665

Hawton, Keith *see* **House, Allan** *et al* 83–92

Healy, David. Marketing of 5-hydroxytryptamine: depression or anxiety? (*Annotation*) 737–742

Healy, Kevin *et al.* Child physical abuse observed. Comparison of families with and without history of child abuse treated in an in-patient family unit 234–237

Hetmar, O. *et al.* Lithium: long-term effects on the kidney. A prospective follow-up study ten years after kidney biopsy 53–58

Hill, Elizabeth *see* **Miller, Bruce L.** *et al* 76–82

Hirsch, Steven *see* **Sensky, Tom** *et al* 792–799, 799–804

Hobbs, Michael. Group psychotherapy (*Reading about...*) 723–725

Hodgson, Richard *see* **Murray, Declan** (BR) 842–844

Hofman, Albert *see* **Duijn, Cornelia M. van** *et al* 471–474

Holden, Neil L. Adoption and eating disorders: a high-risk group? 829–833

Holloway, Frank. Day care in an inner city. I. Characteristics of attenders 805–810

Holloway, Frank. Day care in an inner city. II. Quality of the services 810–816

Holmes, Deborah *et al.* No evidence for a susceptibility locus predisposing to manic depression in the region of the dopamine (D2) receptor gene 635–641

Hopker, S. W. and **Brockington, I. F.** Psychosis following hydatidiform mole in a patient with recurrent puerperal psychosis (BR) 122–123

Hopkins, W. *see* **Taranto, N. E. de** *et al* (C) 714–715

Horiuchi, Masayuki *see* **Otani, Koichi** *et al* (BR) 850–853

House, Allan. Mood disorders in the year after first stroke 83–92

Howard, Robert. All-night television can damage your health (C) 577–578

Hubbard, John W. *see* **Marder, Stephen R.** *et al* 658–665

Hughes, I. C. T. *see* **Pryce, I. G.** *et al* 817–821

Hughes, Timothy *see* **Sensky, Tom** *et al* 792–799, 799–804

Hulst, A. M. van *see* **Stewart, D. E.** *et al* 393–397

Hunter, R. *et al.* Cerebral pharmacodynamics of physostigmine in Alzheimer's disease investigated using single-photon computerised tomography 351–357

Hurry, J. *see* **Bebbington, P. E.** *et al* 33–40, 40–45

Hussain, Y. *see* **Mumford, D. B.** *et al* 379–386

Huws, R. *et al.* Hypersexuality, fetishism and multiple sclerosis (BR) 280–281

Hwang, Sun *see* **Rea, Margaret M.** *et al* 642–647

Ibanez-Rojo, Vicente *see* **Iruela, Luis M.** *et al* (C) 436–437
Inman, William H. W. *see* **Edwards, J. Guy** *et al* 387–392
Iruela, Luis M. *et al.* Panic attacks in schizophrenia (C) 436–437

Jabeen, S. and **Fisher, C. J.** Trazodone-induced transient hypomanic symptoms and their management (BR) 275–278
Jacob, K. S. and **Rajan, I.** Informed consent in India (C) 576
Jacques, Raymond M. and **Cox, Stephen J.** Verapamil in major (psychotic) depression (BR) 124–125
Jawad, Syed Hasan. Survey of psychiatrically ill Asian children (BR) 268–270
Jenkins, M. *see* **Taranto, N. E. de** *et al* (C) 714–715
Jenkins, Peter L. *see* **Farmer, Anne E.** *et al* 177–182
Jenner, Alec *see* **Allen, Jane E.** *et al* 529–533
Johns, Celeste A. *see* **Lieberman, Jeffrey A.** *et al* 503–510
Johns, Celeste A. *see* **Masiar, Stephen J.** (C) 135–136
Johnson, J. *see* **Bamrah, J. S.** (BR) 117–119
Johnstone, E. C. *see* **Collinge, J.** *et al* 624–629
Johnstone, Eve C. *et al.* First episode schizophrenia predicting outcome (C) 713–714
Jones, Lesley *see* **House, Allan** *et al* 83–92
Jones, Peter and **Murray, Robin M.** Genetics of schizophrenia is the genetics of neurodevelopment (*Molecular biology symposium*) 615–623

Kafka, Martin P. Successful treatment of paraphilic coercive disorder (a rapist) with fluoxetine hydrochloride (BR) 844–47
Kane, John *see* **Lieberman, Jeffrey A.** *et al* 503–510
Kaneko, Sunao *see* **Otani, Koichi** *et al* (BR) 850–853
Kantemir, E. *see* **Yazici, O.** *et al* (BR) 847–850
Karki, C. *see* **Rogers, D.** *et al* 97–102
Kasvikis, Yiannis *see* **Noshirvani, Homa F.** *et al* 260–263
Katz, Randy *see* **Farmer, Anne E.** *et al* 177–182
Kean, D. *see* **Young, A. H.** *et al* 158–164
Keep, Peter A. van. Professor Max Hamilton: an apology (C) 434
Kendell, R. E. and **Adams, W.** Unexplained variations in the risk for schizophrenia by month and year of birth 758–763
Kendell, R. E. *see* **Stewart, D. E.** *et al* 393–397
Kennedy, Jo *see* **Dalkin, Tim** (C) 859
Kennedy, Roger *see* **Healy, Kevin** *et al* 234–237
Kerr, T. A. *see* **McClelland, H. A.** *et al* 691–696
Khandelwal, S. K. *see* **Adityanjee** *et al* (C) 289
King, D. J. *et al.* Clinical correlates of neurological soft signs in chronic schizophrenia 770–775
Kingdon, David. Replacing the mental hospital. Community provision for a district's chronically disabled in domestic environments? (BR) 113–117
Kinzl, Johann and **Biebl, Wilfred.** Incestuous abuse in psychiatric patients (C) 719
Kitamura, T. *et al.* Stress and puerperal psychosis (C) 290–291
Klompenhouwer, J. L. *see* **Stewart, D. E.** *et al* 393–397
Ko, Lillian *see* **Luk, Siu-Luen** *et al* 213–221
Kohen, D. and **Mathew, G.** Motor disorders of the mentally handicapped (C) 571
Kohen, Dora. Psychological sequelae of torture (C) 287
Kondo, Tsuyoshi *see* **Otani, Koichi** *et al* (BR) 850–853
Krull, Friedrich *see* **Vartzopoulos, Dimitrios** (BR) 856–857
Kuipers, Liz *see* **Leff, Julian** *et al* (C) 571–572

Lacey, J. Hubert *et al.* Bulimia nervosa: family size, sibling sex and birth order. A catchment-area study 491–494
Ladar, Malcolm and **Morton, Sally.** Benzodiazepine withdrawal syndrome (C) 435–436
Ladefoged, J. *see* **Hetmar, O.** *et al* 53–58
Lam, Dominic *see* **Leff, Julian** *et al* (C) 571–572
Lancashire, Stuart *see* **Creed, Francis** *et al* 183–189
Lane, A. *see* **Collinge, J.** *et al* 624–629
Larkin, C. *see* **Collinge, J.** *et al* 624–629
Larkin, Conall *see* **O'Callaghan, Eadbhard** *et al* 764–769
Larkin, Emmett *see* **Kingdon, David** *et al* (BR) 113–117
Lask, Bryan *see* **Bryant-Waugh, Rachel** 229–233
Lask, Bryan *see* **Turk, Jeremy** (BR) 422–423
Lawson, J. S. *see* **Delva, N. J** *et al* (C) 570
Leach, John. Functional psychoses – are oncogenes involved in their pathogenesis? Some speculations (*Point of view*) 563–568
Leach, M. *see* **Collinge, J.** *et al* 624–629
Leboyer, Marion and **McGuffin, Peter.** Collaborative strategies in the molecular genetics of the major psychoses (*Molecular biology symposium*) 605–610
Lee, Alan S. and **Duggan, Conor F.** British and Australian depression revisited (C) 287–288
Lee, Peter Wing-Ho *see* **Luk, Siu-Luen** *et al* 213–221
Lee, Sing. Anorexia nervosa across cultures (C) 284–285
Lee, Sing. Eating disorders in Asian women (C) 131–132
Lee, Sing. Neuropsychiatric evolution of a case of progressive supranuclear palsy (BR) 273–275
Leff, Julian *et al.* Engagement of relatives in intervention programmes (C) 571–572
Lemon, S. *see* **Burns, Tom** *et al* 685–690
Lesser, Ira M. *see* **Miller, Bruce L.** *et al* 76–82
Leung, Patrick Wing-Leung *see* **Luk, Siu-Luen** *et al* 213–221
Levy, Katharine *see* **Rees, D. A.** (*Molecular biology symposium*) 602–604
Lewis, Glyn and **David, Anthony.** Racism and psychiatry (C) 432–433
Lewis, S. W. *see* **Meadows, G.** *et al* 103–105
Lewis, Shôn *see* **Foerster, Alice** *et al* 171–176
Liddle, Peter F. Commentary on the Modified Rogers scale and the 'conflict of paradigms' hypothesis 337–339
Liddle, Peter F. and **Morris, Danielle L.** Schizophrenic symptoms and frontal lobe performance 340–345
Lieberman, Jeffrey A. *et al.* Effects of clozapine on tardive dyskinesia 503–510
Lieh-Mak, Felice *see* **Luk, Siu-Luen** *et al* 213–221
Lightman, S. L. *see* **Delva, N. J** *et al* (C) 570
Lipkin, Bron. Capgras syndrome (C) 131
Littlewood, Roland. Are British psychiatrists racist? (C) 135
Littlewood, Roland. Ethnic minorities and the psychiatric system (C) 433–434

Littlewood, Roland. The 'new cross-cultural psychiatry' (C) 575–576
Loc'h, C. *see* **Martinot, J. L.** *et al* 346–350
Lofthouse, R. *see* **Collinge, J.** *et al* 624–629
Luk, Siu-Luen *et al.* Behaviour disorder in pre-school children in Hong Kong. A two-stage epidemiological study 213–221
Lund, C. E. *et al.* Motor, volitional and behavioural disorders in schizophrenia. 1: Assessment using the modified Rogers scale 323–327
Lund, C. E. *see* **McKenna, P. J.** *et al* 328–336
Lund, Charles. Psychotic depression: psychoanalytic psychopathology in relation to treatment and management 523–528
Lundmark, Jons *see* **Bengtsson, Bengt-O** *et al* (BR) 853–855

Magni, G. *et al.* Psychiatric diagnoses in ulcerative colitis. A controlled study (BR) 413–415
Mahgoub, Osama Mohammed and **Abdel-Hafeiz, Hassan Babiker**. Pattern of obsessive–compulsive disorder in Eastern Saudi Arabia (BR) 840–842
Mahmood, Tariq. Bromocriptine in catatonic stupor (C) 437–438
Malcolm, Katy *see* **Kingdon, David** *et al* (BR) 113–117
Malsh, C. *see* **Collinge, J.** *et al* 624–629
Manus, André *see* **Monfort, Jean Claude** (C) 570–571
Marder, Stephen R. *et al.* Plasma levels of fluphenazine in patients receiving fluphenazine decanoate. Relationship to clinical response 658–665
Marks, Isaac M. *see* **Noshirvani, Homa F.** *et al* 260–263
Marks, Isaac *see* **Thornicroft, Graham** *et al* 362–367
Martin, A. *see* **Magni, G.** *et al* (BR) 413–415
Martin, J-J *see* **Van Duijn, Cornelia M.** *et al* 471–474
Martin, M. J. *see* **Young, A. H.** *et al* 158–164
Martinot, J. L. *et al.* Estimated density of D_2 striatal receptors in schizophrenia. A study with positron emission tomography and ^{76}Br-bromolisuride 346–350
Masiar, Stephen J. and **Johns, Celeste A.** ECT following clozapine (C) 135–136
Masterton, George. Monthly and seasonal variation in parasuicide. A sex difference. 155–157
Mathew, G. *see* **Kohen, D.** (C) 571
Mauro, P. *see* **Magni, G.** *et al* (BR) 413–415
Mazière, B. *see* **Martinot, J. L.** *et al* 346–350
Mazoyer, B. *see* **Martinot, J. L.** *et al* 346–350
McClelland, H. A. *et al.* Facial dyskinesia: a 16-year follow-up study 691–696
McClelland, R. J. *see* **Doherty, M.** *et al* (BR) 125–127
McConaghy, Neil *see* **Ward, Philip B.** *et al* 534–539
McCreadie, R. G. *et al.* Nithsdale schizophrenia surveys. VIII: Do relatives want family intervention – and does it help? (BR) 110–113
McCreadie, R. G. *et al.* Scottish survey of old long-stay in-patients. R. G. McCreadie *et al* 398–402
McDonald, Carrick. Dementia with parietal signs (C) 859
McDonald, Carrick *see* **Crichton, Paul** (C) 436
McFadyen, Anne *et al.* Impact of a child psychiatry liaison service on patterns of referral 93–96
McGibben, L. and **Ballard, C.** Child and psychiatry liaison services (C) 573
McGibbon, Lawrence *et al.* Anorexia nervosa across cultures (C) 284–285
McGrath, John. Ordering thoughts on thought disorder 307–316
McGuffin, Peter *see* **Leboyer, Marion** (*Molecular biology symposium*) 605–610
McIvor, Ronan J. and **Sinanan, Kenneth**. Buspirone-induced mania (C) 136–137
McKay, Gordon *see* **Marder, Stephen R.** *et al* 658–665
McKenna, P. J. *et al.* Motor, volitional disorders in schizophrenia. 2: 'Conflict of paradigms' hypothesis 328–336
McKenna, P. J. *see* **Lund, C. E.** *et al* 323–327
McKeon, Patrick *see* **McLoughlin, Declan** (BR) 410–413
McLackland, B. M. *see* **Pryce, I. G.** *et al* 817–821
McLoughlin, Declan and **McKeon, Patrick**. Bipolar disorder and cerebral sarcoidosis (BR) 410–413
McQueen, Elizabeth *see* **Ballinger, Brian R.** *et al* 251–254
McQueen, J. K. *see* **Young, A. H.** *et al* 158–164
Meadows, G. *et al.* Assessing schizophrenia in adults with mental retardation. A comparative study 103–105
Mehringer, C. Mark *see* **Miller, Bruce L.** *et al* 76–82
Meijer, Martijn and **Treffers, Philip D. A.** Borderline and schizotypal disorders in children and adolescents 205–212
Metcalfe, A. V. *see* **McClelland, H. A.** *et al* 691–696
Michie, Patricia T. *see* **Ward, Philip B.** *et al* 534–539
Midha, Kamal K. *see* **Marder, Stephen R.** *et al* 658–665
Miller, Bruce L. *et al.* Brain lesions and cognitive function in late-life psychosis 76–82
Miller, Robert. Computerised tomography and schizophrenia (C) 863
Milner, George *see* **Craddock, Bridget** *et al* (C) 130
Mintz, Jim *see* **Marder, Stephen R.** *et al* 658–665
Mirza, S. *see* **Mumford, D. B.** *et al* 379–386
Mogridge, Liz *see* **House, Allan** *et al* 83–92
Mohan, R. N. C. *see* **Ballard, C. G.** *et al* (C) 133
Molivar, A. *see* **Taranto, N. E. de** *et al* (C) 714–715
Monfort, Jean Claude and **Manus, André**. Psychotic depression presenting as ststus epilepticus (C) 570–571
Moniz, Margarida *see* **Azevedo, M. H. Pinto de** (C) 436
Montague, L. R. *see* **Pryce, I. G.** *et al* 817–821
Monteiro, William O. *see* **Noshirvani, Homa F.** *et al* 260–263
Moorey, Stirling *et al.* Factor structure and factor stability of the Hospital Anxiety and Depression scale in patients with cancer 255–259
Morgan, H. G. and **Priest, Pamela**. Suicide and unexpected deaths among psychiatric in-patients. The Bristol confidential inquiry 368–374
Morgenstern, Hal *see* **Glazer, William M.** *et al* 822–828
Morice, Rodney. Selection of controls (C) 862–863
Morris, Danielle L. *see* **Liddle, Peter F.** 340–345
Mortimer, A. M. *see* **Lund, C. E.** *et al* 323–327
Mortimer, A. M. *see* **McKenna, P. J.** *et al* 328–336
Morton, Sally *see* **Ladar, Malcolm** (C) 435–436
Muijen, Matthijs. First episode schizophrenia predicting outcome (C) 713
Mullan, Michael J. *see* **Duijn, Cornelia M. van** *et al* 471–474

UNIVERSITY COLLEGE

Mullen, Paul E. Jealousy: the pathology of passion (*Eliot Slater lecture*) 593–601

Mumford, D. B. *et al.* Bradford Somatic Inventory. Multi-ethnic inventory of somatic symptoms reported by anxious and depressed patients in Britain and the Indo-Pakistan Subcontinent 379–386

Mumford, D. B. *et al.* Sociocultural correlates of eating disorders among Asian schoolgirls in Bradford 222–228

Mumford, David B. Eating disorders in Asians (C) 861

Murphy, D. G. M. Classification and treatment of dysthymia (*Point of view*) 106–109

Murphy, Siobhan M. and **Tyrer, Peter.** Double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence 511–516

Murray, Declan and **Hodgson, Richard.** Polycythaemia rubra vera, cerebral ischaemia and depression (BR) 842–844

Murray, R. M. *see* **Meadows, G.** *et al* 103–105

Murray, Robin M. *see* **Jones, Peter** (*Molecular biology symposium*) 615–623

Murray, Robin *see* **Foerster, Alice** *et al* 171–176

Mutton, Owen *see* **Axford, Shelagh** *et al* (C) 573

Naber, G. *see* **Soyka, M.** *et al* 549–553

Naik, Prakash. How old are the elderly? (C) 575

Naraghi, M. M. *see* **Mumford, D. B.** *et al* 379–386

Neale, T. James *see* **Thomas, Christopher S.** (BR) 119–121

Nemeroff, Charles B. *et al.* Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, β-endorphin and somatostatin 59–63

Ng, Richard *see* **Luk, Siu-Luen** *et al* 213–221

Nikapota, Anula D. Child psychiatry in developing countries. Anula D. Nikapota (*Review article*) 743–751

Noshirvani, Homa F. *et al.* Gender-divergent aetiological factors in obsessive–compulsive disorder 260–263

Oatley, Keith and **Perring, Christina.** Longitudinal study of psychological and social factors affecting recovery from psychiatric breakdowns 28–32

O'Callaghan, Eadbhard *et al.* Season of birth in schizophrenia. Evidence for confinement of an excess of winter births to patients without a family history of mental disorder 764–769

O'Carroll, Ronan. Dementia with parietal signs (C) 859–860

O'Carroll, Ronan *et al.* Parietal signs and sinister prognosis in dementia. A four-year follow-up study 358–361

Oliveros, Sergio C. *see* **Iruela, Luis M.** *et al* (C) 436–437

Ong, S. H. *see* **Tan, T. K. S.** (C) 858

Osborn, Madeline *see* **Creed, Francis** *et al* 183–189

O'Shea, Brian. Anorexia nervosa in the elderly (C) 716–717

Otani, Koichi *et al* (BR) 850–853

Ott, Jurg *see* **Delisi, Lynn E.** *et al* 630–634

Owen, F. *see* **Collinge, J.** *et al* 624–629

Owen, Michael *see* **Foerster, Alice** *et al* 171–176

Özgüroglu, M. *see* **Yazici, O.** *et al* (BR) 847–850

Paillère-Matinot, M. L. *see* **Martinot, J. L.** *et al* 346–350

Patterson, J. *see* **Hunter, R.** *et al* 351–357

Paykel, E. S. *see* **Burns, Tom** *et al* 685–690

Pearce, Gillian L. *see* **Edwards, J. Guy** *et al* 387–392

Peet, Malcolm and **Harvey, Norman S.** Lithium maintenance: 1. A standard education programme for patients 197–200

Peet, Malcolm *see* **Harvey, Norman S.** 200–204

Perring, Christina *see* **Oatley, Keith** 28–32

Petursson, Hannes *see* **Holmes, Deborah** *et al* 635–641

Phaterpekar, H. *see* **Anderson, D. N.** (C) 574–575

Philips, K. *see* **McCreadie, R. G.** *et al* (BR) 110–113

Platts, M. *see* **Mumford, D. B.** *et al* 222–228

Pocock, P. *see* **Rogers, D.** *et al* 97–102

Poirier, M. F. *see* **Martinot, J. L.** *et al* 346–350

Pollack, Simcha *see* **Lieberman, Jeffrey A.** *et al* 503–510

Polley, Richard *see* **Creed, Francis** *et al* 183–189

Poulter, M. *see* **Collinge, J.** *et al* 624–629

Povlsen, U. Juul *see* **Hetmar, O.** *et al* 53–58

Priest, Pamela *see* **Morgan, H. G.** 368–374

Pryce, I. G. *et al.* Nature and severity of disabilities in long-stay psychiatric in-patients in South Glamorgan 817–821

Putten, Theodore van *see* **Marder, Stephen R.** *et al* 658–665

Rajan, I. *see* **Jacob, K. S.** (C) 576

Rafiyah, Gitendra *see* **Bell, Gary** *et al* 554–557

Ram, Ragnatham *see* **Delisi, Lynn E.** *et al* 630–634

Ratnasuriya, R. H. *et al.* Anorexia nervosa: outcome and prognostic factors after 20 years 495–502

Rawson, Nigel S. B. *see* **Edwards, J. Guy** *et al* 387–392

Rea, Margaret M. *et al.* Changes in patient coping style following individual and family treatment for schizophrenia 642–647

Rees, D. A. and **Levy, Katherine.** Molecular genetics of the major psychoses. The role of the Medical Research Council (*Molecular biology symposium*) 602–604

Regan, Adrienne *see* **Bremner, Alexander J.** 244–250

Reid, Andrew H. *see* **Ballinger, Brian R.** *et al* 251–254

Reinstein, Dan Z. *see* **Bell, Gary** *et al* 554–557

Reveley, M. A. *see* **Meadows, G.** *et al* 103–105

Rey, Joseph M. and **Bird, Kevin D.** Sex differences in suicidal behaviour of referred adolescents 776–781

Richards, A. David and **Rose, John S.** Exposure therapy for post-traumatic stress disorder. Four case studies (BR) 836–840

Rifat, Sandra *see* **Flint, Alastair** (C) 866

Roberts, David and **Claridge, Gordon.** Genetic model compatible with a dimensional view of schizophrenia (*Annotation*) 451–456

Roberts, G. W. Schizophrenia: a neuropathological perspective (*Review article*) 8–17

Roberts, Gareth W. *see* **Harrison, Paul J.** (*Review article*) 457–470

Robertson, Bernadette *see* **Moorey, Stirling** *et al* 255–259

Robertson, Lesley *see* **McCreadie, R. G.** *et al* 398–402

Robertson, Mary M. and **Trimble, M. R.** Gilles de la Tourette syndrome in the Middle East. Report of a cohort and a multiply affected large pedigree (BR) 416–419

Robins, Ashley H. *see* **White, Denise A.** (BR) 419–421

Robins, Ashley H. *see* **White, Denise A. C.** (C) 858–859

Rogers, D. *et al.* Motor disorders of mental handicap. An overlap with the motor disorders of severe psychiatric illness 97–102

Rogers, D. *see* **Lund, C. E.** *et al* 323–327

Rollin, Henry. Harveian Society. General paralysis of the insane. Dr Savage (*A hundred years ago*) 138

Rollin, Henry. Hysteria and organic disease (*A hundred years ago*) 438

Rollin, Henry. Music as a remedy (*A hundred years ago*) 578

Rollin, Henry. Nursing of the insane (*A hundred years ago*) 722

Rollin, Henry. Our library table: *Oeuvres Complètes de J. M. Charcot.* Tome IX (*A hundred years ago*) 867

Rollin, Henry. The non-restraint question (*A hundred years ago*) 292

Rooth, F. Graham *see* **Cook, David A. G.** *et al* 238–243

Rose, John S. *see* **Richards, A. David** (BR) 836–840

Rosen, Ismond. Self-esteem as a factor in social and domestic violence 18–23

Rossor, Martin N. *see* **Duijn, Cornelia M. van** *et al* 471–474

Rossor, Rachel *see* **Bell, Gary** *et al* 554–557

Rowden, Linda *see* **Moorey, Stirling** *et al* 255–259

Rowlands, B. J. *see* **Doherty, M.** *et al* (BR) 125–127

Roxborough, H. *see* **Young, A. H.** *et al* 158–164

Russell, G. F. M. *see* **Ratnasuriya, R. H.** *et al* 495–502

Ruszczynski, Stan. *One Flesh: Separate Persons.* Robin Skynner (*Books reconsidered*) 868–870

Ryder, Linda *see* **Farmer, Anne E.** *et al* 177–182

Sachdev, Perminder. Tardive oculogyric crisis and obsessional thoughts (C) 720–721

Saleem, Packeerrowther *see* **Creed, Francis** *et al* 183–189

Saltz, Bruce L. *see* **Lieberman, Jeffrey A.** *et al* 503–510

Sanjeev, D. *see* **Hamer, D.** *et al* 782–784

Schaumann, Helen *see* **Gillberg, Christopher** *et al* 403–409

Scott, Allan I. F. *see* **Stocks, Ruth** 375–378

Scott, J. *see* **Taranto, N. E. de** *et al* (C) 714–715

Sensky, Tom *et al.* Compulsory psychiatric treatment in the community. I. Controlled study of compulsory community treatment with extended leave under the Mental Health Act: Special characteristics of patients treated and impact of treatment 792–799

Sensky, Tom *et al.* Compulsory psychiatric treatment in the community. II. Controlled study of patients whom psychiatrists would recommend for compulsory treatment in the community 799–804

Serra, Eric. Chronic fatigue syndrome (C) 717

Shah, Pritesh J. and **Greenberg, William M.** Tolbutamide and fatal water intoxication (C) 719–720

Shah, T. *see* **Collinge, J.** *et al* 624–629

Shaji, K. S. Educational status and neurological abnormalities in schizophrenia (C) 865–866

Sherrington, Robin *see* **Holmes, Deborah** *et al* 635–641

Shima, S. *see* **Kitamura, T.** *et al* (C) 290–291

Shome, S. *see* **Chadda, R. K.** *et al* (C) 434

Shubsachs, A. P. W. *see* **Huws, R.** *et al* (BR) 280–281

Silveira, W. R. *see* **McGibbon, Lawrence** *et al* (C) 285

Sinanan, Kenneth *see* **McIvor, Ronan J.** (C) 136–137

Sinclair, Janet *see* **Healy, Kevin** *et al* 234–237

Smith, P. H. *see* **Snaith, R. P.** *et al* (C) 132–133

Snaith, R. P. *et al.* Transexualism (C) 132–133

Snaith, R. P. The GHQ and the HAD (C) 433

Snowdon, Claire *see* **Green, Josephine M.** *et al* (C) 865

Snowdon, John. Retrospective case-note study of bipolar disorder in old age 485–490

Souza, F. G. M. and **Goodwin, G. M.** Lithium treatment and prophylaxis in unipolar depression, a meta-analysis 666–675

Soyka, M. *et al.* Prevalence of delusional jealousy in different psychiatric disorders. An analysis of 93 cases 549–553

Stampfer, H. G. *see* **Burvill, P. W.** *et al* 64–71

Standen, Penny J. *see* **Chen, Eric Y. H.** *et al* 517–522

Statham, Helen *see* **Green, Josephine M.** *et al* (C) 865

Steffenburg, Suzanne *see* **Gillberg, Christopher** *et al* 403–409

Stein, Alan *et al.* Relationship between post-natal depression and mother–child interaction 46–52

Stevens, John C. *see* **Allen, Jane E.** *et al* 529–533

Stewart, D. E. *et al.* Prophylactic lithium in puerperal psychosis. The experience of three centres 393–397

Stewart, M. *see* **McCreadie, R. G.** *et al* (BR) 110–113

Stewart, Mary *see* **McCreadie, R. G.** *et al* 398–402

Stocks, Ruth and **Scott, Allan I. F.** What happens to patients who frequently harm themselves? A retrospective one-year outcome study 375–378

Stores, Gregory. Confusions concerning sleep disorders and the epilepsies in children and adolescents (*Annotation*) 1–7

Strachan, Angus M. *see* **Rea, Margaret M.** *et al* 642–647

Strang, John *see* **Gossop, Michael** 697–699

Sturniolo, G. C. *see* **Magni, G.** *et al* (BR) 413–415

Sugawara, M. *see* **Kitamura, T.** *et al* (C) 290–291

Surtees, Paul *see* **Harris, Tirril** *et al* (*Current literature*) 708–712

Sweeney, M. Leonie *see* **Dick, Peter H.** *et al* 24–27

Syrota, A. *see* **Martinot, J. L.** *et al* 346–350

Szabadi, E. *see* **Burrell, M. F.** *et al* (C) 577

Szmukler, G. I. *see* **Ratnasuriya, R. H.** *et al* 495–502

Szulecka, Krystyna *see* **Kingdon, David.** *et al* (BR) 113–117

Tan, T. K. S. and **Elnesr, M.** Is psychiatric training still improving? (C) 134–135

Tan, T. K. S. and **Ong, S. H.** Catatonia and NMS (C) 858

Taranto, N. E. de *et al.* Gender-identity clinic patients. (C) 714–715

Tastaban, Y. *see* **Yazici, O.** *et al* (BR) 847–850

Taylor, P. J. *see* **Huws, R.** *et al* (BR) 280–281

Tennant, C. *see* **Bebbington, P. E.** *et al* 33–40, 40–45

Terwilliger, Joseph D. *see* **Delisi, Lynn E.** *et al* 630–634

Thomas, Christopher S. and **Neale, T. James.** Organic manic syndrome associated with advanced uraemia due to polycystic kidney disease. (BR) 119–121

Thomas, Phil *see* **Creed, Francis** *et al* 183–189

Thornicroft, Graham. Social deprivation and rates of treated mental disorder. Developing statistical models to predict psychiatric service utilisation 475–484

Thornicroft, Graham *et al.* In-patient behavioural psychotherapy unit. Description and audit 362–367

Toda, M. A. *see* **Kitamura, T.** *et al* (C) 290–291

Tomenson, Barbara *see* **Creed, Francis** *et al* 183–189

Travers, Raymond. Buspirone in detoxification (C) 133–134

Treffers, Philip D. A. *see* **Meijer, Martijn** 205–212

Trimble, M. R. *see* **Robertson, Mary M.** (BR) 416–419

Tsai, L. *see* **Ghaziuddin, M.** (BR) 127–129

Tsakiris, Fivos *see* **Noshirvani, Homa F.** *et al* 260–263

Tsuang, Ming T. Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizoaffective disorders 165–170

Tunmore, Robert *see* **Moorey, Stirling** *et al* 255–259

Turk, Jeremy and **Lask, Bryan**. Pisa syndrome in an adolescent on neuroleptic medication (BR) 422–423

Turkington, Douglas *see* **Kingdon, David** *et al* (BR) 113–117

Turner, T. *see* **Meadows, G.** *et al* 103–105

Twena, D. *see* **Taranto, N. E. de** *et al* (C) 714–715

Tyrer, Peter *see* **Murphy, Siobhan M.** 511–516

Tyrer, Stephen *et al.* Prescribing in mental handicap hospitals (C) 283

Tyrrell, Philippa *see* **Wilson, Ken** *et al* (*Current literature*) 558–562

Üçok, A. *see* **Yazici, O.** *et al* (BR) 847–850

Vandenberghe, Anton *see* **Duijn, Cornelia M. van** *et al* 471–474

Vartzopoulos, Dimitrios and **Krull, Friedrich**. Dependence on monoamine oxidase inhibitors in high dose (BR) 856–857

Völcker, A. *see* **Soyka, M.** *et al* 549–553

Waddington, J. L. *see* **King, D. J.** *et al* 770–775

Waddington, John L. *see* **O'Callaghan, Eadbhard** *et al* 764–769

Waldron, G. *see* **McCreadie, R. G.** *et al* (BR) 110–113

Walinder, Jan *see* **Bengtsson, Bengt-O.** *et al* (BR) 853–855

Walker, Nigel. Dangerous mistakes (*Maudsley lecture*) 752–757

Walshe, David *see* **O'Callaghan, Eadbhard** *et al* 764–769

Walter, Garry. Failure to convulse with ECT (C) 716

Ward, Philip B. *et al.* Auditory selective attention and event-related potentials in schizophrenia 534–539

Warlow, Charles *see* **House, Allan** *et al* 83–92

Watkins, S. E. *see* **Pryce, I. G.** *et al* 817–821

Watson, Maggie *see* **Moorey, Stirling** *et al* 255–259

Watson, P. *see* **McClelland, H. A.** *et al* 691–696

Weaver, Christine M. *see* **Cook, David A. G.** *et al* 238–243

Webb, Y. *see* **Clifford, P.** *et al* 190–196

Wheatley, David. Depression and the menopause (C) 431–432

Wheatley, David and **Bass, David**. Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial (*Current literature*) 264–267

White, Denise A. C. and **Robins, Ashley H.** Catatonia: harbinger of the neuroleptic malignant syndrome (BR) 419–421

White, Denise A. C. and **Robins, Ashley H.** Catatonia and NMS (C) 858–859

White, T. *see* **Brown, K. W.** (BR) 270–272

Whitehouse, A. M. *see* **Mumford, D. B.** *et al* 222–228

Whittick, Janice *see* **O'Carroll, Ronan** *et al* 358–361

Wilcox, James Allen. Pituitary microadenoma presenting as panic attacks (BR) 426–427

Wilson, K. C. M. *see* **Green, B. M.** (C) 291–292

Wilson, A. *see* **King, D. J.** *et al* 770–775

Wilson, David. Systemic lupus erythematosus in a woman with mental handicap (BR) 427–429

Wilson, Ken *et al.* Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease (*Current literature*) 558–562

Winokur, George *see* **Cook, Brian L.** *et al* 72–75

Wong, Keith *see* **Miller, Bruce L.** *et al* 76–82

Wong, Virginia C. N. *see* **Luk, Siu-Luen** *et al* 213–221

Wressell, Susan *see* **Tyrer, Stephen** *et al* (C) 283

Wright, Padraig. Tardive dyskinesia and HLA (C) 863–864

Wyper, D. J. *see* **Hunter, R.** *et al* 351–357

Yazici, O. *et al.* Spontaneous improvement of tardive dystonia during mania (BR) 847–850

Yeung, C. Y. *see* **Luk, Siu-Luen** *et al* 213–221

Young, A. H. *et al.* MRI study of schizophrenia. Brain structure and clinical symptoms 158–164

Zaudig, Michael *see* **Bose, Michael J. von** (BR) 278–280

Zibin, Terry *see* **Byrne, Alan** (C) 578

PART III. BOOK REVIEWS

AGGRESSION

- **Jaffe, Peter G.**, **Wolfe, David A.** and **Wilson, Susan Kaye**. Children of battered women. (Rachel Leheup) 587
- **Pulkkinen, Lea** and **Ramirez, J. Martin** (eds). Aggression in children. (Roy Howarth) 150
- **Stordeur, Richard A.** and **Stille, Richard**. Ending men's violence against their partners. (Stephen P. Reilly) 732–733

AIDS

- Plant, Martin (ed.). Aids, drugs and prostitution. (R. P. Brettle) 147

ANXIETY

- **Kennerly, Helen**. Managing anxiety: a training manual. (Paul Gilbert) 300
- **Roth, Sir Martin, Noyes, R. Jr.** and **Burrows, Graham D.** (eds). Handbook of anxiety, Vol. 1: Biological, clinical and cultural perspectives. (Philip Cowan) 448–449

Roth, Sir Martin, Noyes, R. Jr and **Burrows, Graham D.** (eds). Handbook of anxiety, Vol. 2: Classification, etiological factors and associated disturbances. (M. G. Gelder) 449

ART THERAPY

Liebermann, Marian (ed.). Art therapy in practice. (Louis Marteau) 585–586

ATTENTION DISORDERS

Goldstein, Sam and **Goldstein, Michael**. Managing attention disorders in children: a guide for practioners. (Aris Ambelas) 447–448

CANCER

Holland, Jimmie and **Rowland, Julia** (eds). Handbook of psychooncology: psychological care of the patient with cancer. (Amanda J. Ramirez) 149–150

CHILD ABUSE

British Psychological Society – Frude, Neil, Peake, Anne, Sambrooks, Jean, Stratton, Peter and **Cullen, Chris**. Psychologists and child sexual abuse. (Charmian Bollinger) 726–727

Li, C. K., West, D. L. and **Woodhouse, T. P.** Children's sexual encounters with adults. (Michael King) 728

Research Team. Northern Ireland. Child sexual abuse in Northern Ireland. (Michael King) 728

CHILD AND ADOLESCENT PSYCHIATRY

Barker, Philip. Clinical interviews with children and adolescents. (Dora Black) 298

Chess, Stella and **Hertzig, Margaret** (eds). Annual progress in child psychiatry and child development 1989. (Israel Kolvin) 727–728

Chiland, Colette and **Young, J. Gerald** (eds). Why children reject school: views from seven countries. (Ian Berg) 735

Garfinkel, Barry D. *et al*. Psychiatric disorders in children and adolescents. (Simon Gowers) 150–151

Kesterbaum, Clarice J. and **Willims, Daniel T.** (eds). Handbook of children and adolescents. Vols I & II. (Philip Graham) 727

Kreilkamp, Thomas. Time-limited intermittent therapy with children and families. (Alyson Hall) 298–299

Mussen, Paul Henry, Conger, John Janeway, Kagan, Jerome and **Huston, Aletha Carol**. Child development and personality. (John C. Coleman) 878

CHILD PSYCHIATRY

Judd, Dorothy. Give sorrow words: working with a dying child. (Michael Prendergast) 443

Trad, Paul V. Conversations with pre-school children. Uncovering developmental patterns. (Stephen Isaacs) 297

Trad, Paul V. The preschool child: assessment, diagnosis and treatment. (Gillian Forrest) 586

COMPUTING

West, Robert, Christie, Margaret and **Weinman, John** (eds). Microcomputers, psychology and medicine. (Colin Cooper) 303–304

CROSS-CULTURAL PSYCHIATRY

Leff, Julian. Psychiatry around the Globe: a transcultural view (2nd edn). (John Cox) 142

Prins, Herschel. Bizarre behaviours. (W. H. Trethowan) 589–590

DEMENTIA

Katona, C. L. A. (ed.). Dementia disorders: advances and prospects. (Jane Garner) 144–145

DEPRIVATION

Kolvin, I., Miller, F. J. W., Scott, McL., Gatzanis, S. R. M. and **Fleeting, M.** Continuities of deprivation? The Newcastle 1000 family study. (Marian Perkins) 726

DOWN SYNDROME

Cichetti, Dante and **Beeghly, Marjorie** (eds). Children with Down syndrome: a developmental perspective. (Aris Ambelas) 878

EATING DISORDERS

Anderson, Arnold E. (ed.) Males with eating disorders (Eating disorders monograph series. No. 4). (Neil L. Holden) 152

Williamson, Donald A. Assessment of eating disorders. Obesity, anorexia and bulimia nervosa. (Anthony H. Fry) 444–445

ECONOMIC PSYCHOLOGY

Grunert, Klaus G. and **Olander, Folke**(eds). Understanding economic behaviour. (Alan Budd) 142–143

EPILEPSY

Bolwig, Tom G. and **Trimble, Michael R.** (eds). The clinical relevance of kindling. (David Chadwick) 590

Sillanpää, Matti, Johannessen, Svein I., Blennow, Gösta and **Dam, Mogens**. Paediatric epilepsy. (D. F. Scott) 729

ETHICS

Group for the Advancement of Psychiatry Committee on medical education. A casebook in psychiatric ethics. (David Tait) 877

EXAMINATIONS

Puri, Basant K. and **Sklar, Jon**. Examination notes for the MRCPsych Part 1. (David Julier) 148

FORENSIC PSYCHIATRY

Cooke, David J., Baldwin, Pamela J. and **Howison, Jacqueline**. Psychology in prisons. (Heinz Albrecht) 587–588

Melton, Gary B., Petrila, John, Poythress, Norman G. and **Slobogin, Christopher**. Psychological evaluations for the courts. (Heinz Albrecht) 879

O'Connell, Michael, Donaldson, Craig R. and **Leberg, Eric**. Working with sex offenders. (Heinz Albrecht) 448

Steadman, Henry, McCarty, Dennis W. and **Morrissey, Joseph P.** The mentally ill in jail. (Heinz Albrecht) 447

GENERAL PSYCHIATRY

Cooper, Brian and **Helgason, Thomas** (eds). Epidemiology and the prevention of mental disorders. (Glynn Harrison) 588

Hawton, Keith and **Cowen, Philip** (eds). Dilemmas and difficulties in the management of psychiatric patients. (Christopher Thompson) 733

Perry, Samuel, Frances, Allen and **Clarkin, John** A. DSM–III–R casebook of treatment selection. (Peter Tyrer) 730–731

Sainsbury, M. J. and **Lambeth, L. G.** Sainsbury's key to psychiatry (4th edn). (Robert Kerwin) 878–879

Talbot, J. A. *et al* (eds). Yearbook of psychiatry and applied mental health 1989. (R. J. Daly) 145

GROUP THERAPY

Ganzarain, Ramon. Object relations group psychotherapy: the group as an object, a tool and a training base. (Richard Carvalho) 874

Skynner, Robin, edited by **Schlapobersky, John R.** Explorations with families: group analysis and family therapy. (Peter Loader) 305

Wanigaratne, Shamil, Wallace, Wendy, Pullin, Jane, Keaney, Francis and **Farmer, Roger**. Relapse prevention for addictive behaviours: a manual for therapists. (Michael Farrell) 875

HISTORY

Gay, Peter. (Introduction) Sigmund Freud and art: his personal collection of antiquities. (Hugh Freeman) 153

Rollin, Henry R. Festina lente: a psychiatric odyssey. (Allan Beveridge) 143

HYPNOTISM

Erickson, Milton H. *et al.* The practical application of medical and dental hypnosis. (David Waxman) 147–148

Weitzenhoffer, André M. The practice of hypnotism. Vols 1, 2: traditional, semi-traditional and non-traditional techniques and phenomenology. (David L. Pedersen) 445–446

HYSTERIA

Slavney, Phillip R. Perspectives on 'hysteria'. (Harold Merskey) 583

LIAISON PSYCHIATRY

Fallowfield, Lesley. The quality of life. The missing measurement in health care. (Oscar Daly) 733–734

Hale, M. S. (ed.). Advances in psychosomatic medicine – Vol. 20: Methods in teaching consultation – Liaison psychiatry. (Richard Mayou) 871–872

MENTAL HANDICAP

Brown, Steven and **Wistow, Gerald** (eds). The roles and tasks of community handicap teams. (Joan Bicknell) 730

Dosen, Anton and **Menolascino, Frank** (eds). Depression in mentally retarded children and adults. (Andrew H. Reid) 729

Segal, Stanley S. (ed.) Creative arts and mental disability: the role of the creative arts in the development of young people and adults with mental handicaps and severe profound or multiple disabilities. (Geraldine Holt) 729–730

MENTAL HEALTH

Hirschorn, Larry. The workplace within: psychodynamics of organisational life. (Lorna Arblaster) 735

Sherlock, Harley. Cities are good for us. (Hugh Freeman) 148

MOOD DISORDERS

Bech, Per and **Coppen, Alec** (eds). The Hamilton scale. (David Healy) 877

Burton, S. W. and **Akiskal, H. S.** (eds). Dysthymic disorder. (J. Fahy) 143–144

Gut, Emmy. Productive and unproductive depression: success or failure of a vital process. (Graeme McGrath) 302–303

Kumar, R. and **Brockington, I. F.** (eds). Motherhood and mental illness: 2. Causes and consequences. (Patricia Ainsworth) 304–305

Thompson, C. and **Silverstone, T.** (eds) Seasonal affective disorder. (M. W. P. Carney) 296

Tsuang, Ming T. and **Faraone, Stephen V.** The genetics of mood disorders. (Michael C. O'Donovan) 875–876

MUTISM

Lebrun, Yvan. Mutism. (Chris Hollis) 872–873

NEUROCHEMISTRY

Rose, F. Clifford (ed.). The control of the hypothalamo–pituitary adrenocortical axis. (Nicol Ferrier) 144

NEUROSES

Tyrer, Peter. Classification of neuroses. (Terry Birchmore) 442

PAIN

Millar, Thomas. Chronic pain: Vols 1, 2. (David G. Gaylard) 871

PERSONALITY DISORDERS

Millon, Theodore. Towards a new personality. (Paul Kline) 731

Rinsley, Donald E. Developmental pathogenesis and treatment of borderline and narcissistic personalities. (Mark Berelowitz) 445

PHARMACOLOGY

Devane, C. Lindsay. Fundamentals of monitoring psychoactive drug therapy. (Stephen J. Cooper) 145–146

Dhal, S. G. and **Gram, L. F.** (eds). Clinical pharmacology in psychiatry from molecular studies to clinical reality. (John Cookson) 146

Gershon, S. and **Pohl, R.** (eds). The biological basis of psychiatric treatment. (R. E. B. White) 301–302

Gorman, Jack. The essential guide to psychiatric drugs. (John Pollitt) 589

Hollister, Leo H. and **Csernansky, John G.** Clinical pharmacology of psychotherapeutic drugs (3rd edn). (Christos Pantelis) 588–589

PSYCHOANALYSIS

Field, Kay, Cohler, Bertram J. and **Wool, Glorye**. Learning and education: psychoanalytic perspectives. (Nicola Blandford) 299–300

Grolnick, Simon. The work and play of Winnicott. (C. Lucey) 872

Grunberger, Bela. Narcissism: psychoanalytic essays. (Brian O'Shea) 150
Kreuger, David W. Body self and psychological self: a developmental and clinical integration of disorders of the self. (Michael R. Pokorny) 302
Modell, Arnold. Other times, other realities. Towards a theory of psychoanalytic treatment. (Stephen Wilson) 583–584
Moore, Burness and **Fine, Bernard** (eds). Psychoanalytic terms and concepts. (Phil Mollon) 151–152
Sandler, Joseph (ed.). Dimensions of psychoanalysis. (Brian Lake) 584
Seinfeld, Jeffrey. The bad object: handling the negative therapeutic reaction in psychotherapy. (Teresa Black) 152–153

PSYCHOLOGY
Archer, John and **Browne, Kevin** (eds). Human aggression: naturalistic approaches. (Paul Bowden) 587
Cohen, David. Essential psychology: psychology clearly explained and defined. (Eric Button) 879
Gainotti, G. and **Caltagorone, C.** (eds). Emotions and the dual brain. (Anthony David) 876–877
Gilbert, Paul. Human nature and suffering. (Lena Rustin) 443
Hale, Malcolm. The mind: its origin, evolution, structure and functioning. An independent study of the basic mental processes. (Trian Fundulus) 149
Rachman, S. J. Fear and courage (2nd edn). (Mark Morris) 447
Schroeder, Stephen R. (ed.). Ecobehavioural analysis and developmental disabilities: the twenty-first century. (Francesca Happe) 443–444
Swaan, Abram De. Management of normality. (Margaret R. Hilton) 873

PSYCHOTHERAPY
Butcher, James. MMPI-2 in psychological treatment. (Paul Kline) 586
Cotton, Dorothy H. G. Stress management: an integrated approach to therapy. Psychosocial stress series No. 17. (R. A. Williams) 300–301
Dryden, Windy and **Norcross, John C.** (eds). Eclecticism and integration in counselling and psychotherapy. (Duncan Cramer) 873–874
Fossum, Merie A. and **Mason, Marilyn J.** Facing shame: families in recovery. (Peter Fullerton) 299
Glantz, Kalman and **Pearce, John K.** Exiles from Eden: psychotherapy from an evolutionary perspective. (Tom Murphy) 296–297
Graham, John H. MMPI-2 assessing personality and psychotherapy. (Paul Kline) 586
Ogden, Thomas H. The primitive edge of experience. (Brian V. Martindale) 444
Paul, I. H. The craft of psychotherapy. Twenty-seven studies. (Mark Aveline) 732
Stricker, George and **Fisher, Martin** (eds). Self-disclosure in the therapeutic relationship. (Hans Cohn) 303
Zeig, Jeffery K. and **Gilligan, Stephen G.** (eds). Brief therapy: myths, methods and metaphors. (Else Guthrie) 874–875

SCHIZOPHRENIA
Bentall, Richard P. (ed.) Reconstructing schizophrenia. (Chris Frith) 585
Weller, Malcolm (ed.). International perspectives in schizophrenia – biological, social and epidemiological findings. (Robert I. Cohen) 584–585

SEXOLOGY
Money, John and **Lamacz, Margaret**. Vandalized lovemaps: paraphiliac outcome of seven cases in paediatric sexology. (Dinesh Bhugra) 711–712

STATISTICS
Bryman, Alan and **Cramer, Duncan**. Quantitative data analysis for social scientists. (Brian Everitt) 590
Dunn, G. Design and analysis of reliability studies. The statistical evaluation of measurement errors. (E. B. Faragher) 146–147

STRESS
Figley, Charles R. and **Leventman, Seymour**. Strangers at home: Vietnam veterans since the war. (Jonathon Bisson) 734
Johnstone, Marie and **Wallace, Louise** (eds). Stress and medical procedures. (Christopher Bass) 301
Kulaka, Richard A. Kulka *et al.* Trauma and the Vietnam war generation: report of findings from the National Vietnam Veterans Readjustment Study. (Douglas S. C. Gamble) 304
Maida, Carl A., Gordon, Norma A. and **Farberow, Norman L.** The crisis of competence: transitional stress and the displaced worker. (Douglas G. Fowlie) 446
Parry, Glenys. Coping with stress. (Nigel Beail) 449

SUBSTANCE ABUSE
Ghodse, Hamid and **Maxell, Douglas**. Substance abuse and dependence. (Duncan Raistrick) 734–735

SUICIDE
Lester, David (ed.). Current concepts of suicide. (Christopher Vassilas) 876
MacLean, George (ed.) with contributions from **Davidson, S., Joffe, R. T., Offord, D. R.** and **Pfeffer, C. R.** Suicide in children and adolescents. (L. G. Scarth) 297–298

Supplement 10, Volume 158

PART I. SUBJECTS

Adolescence
  - Adolescence and promiscuity: psychopathology. Estela V. Welldon 88–89
  - Services. Fiona Subotsky 18–19

Alcohol. Alcohol and drug-misuse among women – an overview. Edna Oppenheimer 36–44

Anxiety. 'Biological clock' and 'success anxiety'. Estela V. Welldon 89–90

Autonomy and reproduction. Ethical issues. Carol C. Nadelson 12–14

Carers of dementia sufferers. Gender differences. Robin G. Morris *et al* 69–74

Childhood
  - Adult sequelae of sexual abuse. Carol Sheldrick 55–62
  - Services. Fiona Subotsky 18
  - Sexual abuse, disordered personality and eating disorders. L. McClelland *et al* 63–68

Crime. Women as perpetrators and victims. A sociological perspective. Frances M. Heidensohn 50–54

Dementia. Gender differences in carers. Robin G. Morris *et al* 69–74

Depression. Depression in women. E. S. Paykel 22–29

Doctors
  - Conflicting roles. Carol C. Nadelson 10–11
  - Sexual interactions. Carol C. Nadelson 14–15

Drugs
  - Alcohol and drug misuse – an overview. Edna Oppenheimer 36–44
  - Psychotropic-drug prescribing. Heather Ashton 30–35

Eating disorders
  - Bulimia, anorexia and self-mutilation. Estela V. Welldon 88–89
  - Sexual abuse and disordered personality. L. McClelland *et al* 63–68

Editors' introduction. Lyn Pilowsky *et al* 7–8

Epidemiology
  - Depression. E. S. Paykel 25–26
  - Use of tranquillisers. Heather Ashton 31

Ethics. Emerging issues. Carol C. Nadelson 9–16

Gender differences *see* **Sex differences**

Help-seeking behaviour. Depression. E. S. Paykel 23

HIV infection. Risks. Edna Oppenheimer 40

Informed consent. Doctor – patient relationship. Carol C. Nadelson 11–12

Introduction. Editors' introduction. Lyn Pilowsky *et al* 7–8

Life stress and post-partum psychosis. A preliminary report. M. N. Marks *et al* 45–49

Long-term psychiatric patients
  - Sex differences in service usage. Rachel E. Perkins and Len A. Rowland 75–79
  - Where do people with long-term mental health problems live? A comparison of the sexes. Alison M. Conning and L. A. Rowland 80–84

Marriage, sexual relationships and separation. Services. Fiona Subotsky 19

Medical ethics. Emerging issues. Carol C. Nadelson 9–16

Menstruation and fertility. Service issues. Fiona Subotsky 19

Mental health services. Issues for women in mental health service development. Fiona Subotsky 17–21

Middle age. Service issues. Fiona Subotsky 19–20

Motherhood
  - Psychology and psychopathology in women. Estela V. Welldon 90–91
  - Services. Carol C. Nadelson 19

Old age. Services. Fiona Subotsky 20

Paternalism. Medical policies. Carol C. Nadelson 11–12

Perpetrators and victims of crime. A sociological perspective. Frances M. Heidensohn 50–54

Personality disorders. Sexual abuse and eating disorders. L. McClelland *et al* 63–68

Pregnancy and childbirth
  - Alcohol and drug misuse. Edna Oppenheimer 39–40
  - Psychology and psychopathology. Estela V. Welldon 87–88
  - Services. Fiona Subotsky 19

Promiscuity and prostitution. Psychology and psychopathology in women. Estela V. Welldon 88–89

Psychoanalysis. Psychology and psychopathology in women. A psychoanalytic perspective. Estela V. Welldon 85–92

Psychoses. Life stress and post-partum psychosis. M. N. Marks *et al* 45–49

Reproduction and autonomy. Ethical issues. Carol C. Nadelson 12–14

Roles
  - Doctors, patients and society. Carol C. Nadelson 10–11
  - Gender differences in expectations of carers of dementia sufferers. Robin G. Morris *et al* 71–73

Sequelae, adult. Child sexual abuse. Carol Sheldrick 55–62
Service usage. Sex differences in long-term psychiatric care. Rachel E. Perkins and Len A. Rowland 75–79
Sex differences
  Carers of dementia sufferers. Robin G. Morris *et al* 69–74
  Depression. E. S. Paykel 22–23
  Perpetrators and victims of crime. A sociological perspective. Frances M. Heidensohn 50–54
  Psychotropic-drug prescribing. Heather Ashton 30–35
  Service usage in long-term psychiatric care. Rachel E. Perkins and Len A. Rowland 75–79
  Where do people with long-term mental health problems live? A comparison of the sexes. Alison M. Conning and L. A. Rowland 80–84
Sexual abuse
  Adult sequelae of child abuse. Carol Sheldrick 55–62
  Disordered personality and eating disorders. L. McClelland *et al* 63–68
Sexual relationships
  Doctors/patients. Carol C. Nadelson 14–15
  Marriage and separation: services. Fiona Subotsky 19
Social factors
  Causes of depression. E. S. Paykel 25
  Consequencies and antecedents of alcohol and drug misuse. Edna Oppenheimer 40–41

Treatment and rehabilitation. Alcohol and drug misuse. Edna Oppenheimer 41–43

Victims of crime. A sociological perspective. Frances M. Heidensohn 50–54

PART II. CONTRIBUTORS

Ashton, Heather. Psychotropic-drug prescribing for women 30–35

Checkley, S. A. *see* **Marks, M. N.** *et al* 45–49
Conning, Alison M. and **Rowland, L. A.** Where do people with long-term mental health problems live? A comparison of the sexes 80–84

Davies, Kath S. *see* **Morris, Robin G.** *et al* 69–74

Fahy, T. *see* **McClelland, L.** *et al* 63–68

Heidensohn, Frances. Women as perpetrators and victims of crime. A sociological perspective 50–54

Kumar, R. *see* **Marks, M. N.** *et al* 45–49

McClelland, L. *et al.* Sexual abuse, disordered personality and eating disorders 63–68
Marks, M. N. *et al.* Life stress and post-partum psychosis. A preliminary report 45–49
Moodley, Parimala *see* **Pilowsky, Lyn** *et al* 7–8
Morris, Lorna W. *see* **Morris, Robin G.** *et al* 69–74
Morris, Robin G. *et al.* Gender differences in carers of dementia sufferers 69–74
Mynors-Wallis, L. *see* **McClelland, L.** *et al* 63–68

Nadelson, Carol C. Emerging issues in medical ethics 9–16

Oppenheimer, Edna. Alcohol and drug-misuse among women – an overview 36–44
O'Sullivan, Geraldine *see* **Pilowsky, Lyn** *et al* 7–8

Palazidou, Eleni *see* **Pilowsky, Lyn** *et al* 7–8
Paykel, E. S. Depression in women 22–29
Perkins, Rachel E. and **Rowland, Len A.** Sex differences in service usage in long-term psychiatric care 75–79
Pilowsky, Lyn *et al.* Editors' introduction 7–8

Ramana, Rajini *see* **Pilowsky, Lyn** *et al* 7–8
Rowland, L. A. *see* **Conning, Alison M.** 80–84
Rowland, Len A. *see* **Perkins, Rachel E.** 75–79

Sheldrick, Carol. Adult sequelae of child sexual abuse 55–62
Subotsky, Fiona. Issues for women in the development of mental health services 17–21

Treasure, J. *see* **McClelland, L.** *et al* 63–68

Welldon, Estela. Psychology and psychopathology in women. A psychoanalytic perspective 85–92
Wieck, A. *see* **Marks, M. N.** *et al* 45–49
Woods, Robert T. *see* **Morris, Robin G.** *et al* 69–74

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J. Gabe
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P. Hayward
D. Healy
B. Heine
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